Formulation and evaluation of mucoadhesive films for treatment of vaginal candidiasis

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Research Article

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Abstract

Recurrent vulvovaginal candidiasis is long-term condition that can severely affect the quality of life of affected women. Worldwide, recurrent vulvovaginal candidiasis affects about 138 million women annually (range 103–172 million), with a global annual prevalence of 3871 per 100 000 women; 372 million women are affected by recurrent vulvovaginal candidiasis over their lifetime. Along with oral antifungals, intravaginal therapy represents the route of choice for both local and systemic effects, which is patient convenient and effective alternate for vaginal infections. Mucoadhesive vaginal films of itraconazole were formulated and optimized using hydroxypropylmethylcellulose CP 50, Eudragit RS 100, PEG 400 and Soluplus ®, solvent casting technique using hydroxyl propylcellulose and sodium alginate as polymers. Propylene glycol and polyethylene glycol-400 were evaluated as plasticizers. Prepared films were evaluated for weight, thickness, uniformity of weight, disintegration time of films, drug content determination, in vitro drug release studies, mechanical strength and antifungal activity. The films exhibited controlled release over more than 24 hrs. From the study it was concluded that the films containing 25 mg itraconazole exhibited satisfactory swelling, an optimum mechanical strength and promising drug release. The formulation was found to be suitable candidate for the antifungal activity of vaginal films for therapeutic use.

INTRODUCTION

Vulvovaginitis is condition identified as inflammation of the vulva and vagina. It is a common clinical condition observed in general practice. Acute candida vulvovaginitis (ACV) usually occurs in normal healthy women and those consuming oral contraceptive or antibiotic or immunosuppressive chemotherapy or associated with clinical conditions such as diabetes, HIV disease. The causes may be infective or non-infective. Most infective cases are caused by candidiasis or bacterial vaginosis. Vulvovaginal candidiasis is usually due to *Candida albicans* which is part of the normal vaginal microbiome of women of reproductive age. Candidal vulvovaginitis is indicated by inflammatory changes in the vaginal and vulvar epithelium associated with typically thick and adherent discharge, or with excoriations, "external" dysuria, vaginal itching, vaginal burning, dyspareunia, or swelling[1].

Candidal vulvovaginitis has been reported as third of all cases of vulvovaginitis in reproductive-aged women. It has also been reported that 70% of women had candidal vulvovaginitis at some point in their lifetimes[2]. Recurrent vulvovaginal candidiasis is a debilitating, long-term condition that can severely affect the quality of life of affected women. Worldwide, recurrent vulvovaginal candidiasis affects about 138 million women annually (range 103–172 million), with a global annual prevalence of 3871 per 100 000 women; 372 million women are affected by recurrent vulvovaginal candidiasis over their lifetime[3]. About 8% of women suffer recurrent candidal vulvovaginitis. The most common responsible pathogen is *C. albicans* (in about 90% of cases), with most of the remaining cases caused by *Candida glabrata*[3]. The 25–34-year age group has the highest prevalence (9%). By 2030, the population of women with recurrent vulvovaginal candidiasis each year is estimated to increase to almost 158 million. The high

prevalence, substantial morbidity, and economic losses of recurrent vulvovaginal candidiasis require better solutions and improved quality of care for affected women[4].

The condition is clinically managed with antifungal medications. Along with oral antifungals, intravaginal therapy represents the route of choice for both local and systemic effects. The presence of dense network of blood vessels has made vagina an excellent route of drug delivery for both systemic and local effect[5]. Vaginal drug delivery system is used for the treatment of local diseases affecting the vagina like candidiasis. Several conventional drug delivery systems are used for treatment of vaginal infections such suspensions, cream, vaginal tablets, pessaries, vaginal suppositories and solutions, but these conventional formulations cannot maintain effective drug concentration for prolonged period of time inside the vaginal cavity due to their short residence time at the site of administration. The vaginal route is less preferable in terms of convenience. Tablets and gels associated with limitation of leakage and messiness cause inconvenience to users, leading to poor patient compliance. The permeability of the vagina is strongly influenced by the estrogen concentration, which can influence the pharmacokinetics of drugs designed for systemic action[4].

Hence the present work has been undertaken to target an antifungal drug to the vaginal mucosa[6]. The efficacy of vaginal mucoadhesive drug delivery systems (DDS) is affected by the biological environment and the properties of the polymer and the drug. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. Dosage forms designed for mucoadhesive vaginal drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Antifungal drug chosen for the study is itraconazole (ITR).

Within the past decade orally administered and absorbable azoles have become available, initially ketoconazole, subsequently fluconazole and most recently itraconazole. Azoles are considered safe in breastfeeding women. ITR has excellent in vitro activity against *Candida albicans.* This suggests that it would be efficacious in the treatment of candida vulvovaginitis. It acts by inhibiting the fungal cytochrome P-450 dependent enzyme lanosterol 14-α-demethylase[7]. When this enzyme is inhibited, it blocks the conversion of lanosterol to ergosterol, which disrupts fungal cell membrane synthesis. ITR is an orally active triazole antifungal agent with enhanced activity against Candida species. It is well absorbed following oral administration with a meal, concentrates in tissues, and has a long elimination half-life and a good safety profile. However, the resulting high systemic concentration of ITZ has been reported to cause nephrotoxicity and hepatic damage, as well as various reproductive complications[8]. Therefore, topical administration of ITZ can be advantageous for site-specific delivery, with fewer side effects than oral administration. The mucoadhesive vaginal drug delivery system of ITR was formulated and evaluated to increase retention time, enhanced bioavailability and improved patient compliance for the treatment of vaginal candidiasis.

MATERIALS & METHODS

2.1 Materials

Itraconazole Pellets were obtained from Glenmark Ltd, India.; Hydroxy propyl methyl cellulose E15, Hydroxy Ethyl cellulose, Ethyl Cellulose, Hydroxy propyl methyl cellulose CP 50, HPMC K4M from Colorcon Asia Private Limited, India; Hydroxy propyl cellulose, HP, MC metolose from Shin-Etsu Chemical Co. Ltd, India.; Sodium alginate, Propylene glycol, Sodium acetate, Potassium hydrogen phthalate, Potassium bromide from Merck Ltd, India.; Eudragit L 100, Eudragit RS 100, PEG 400 from Evonik Pharma; PVP K 30, Soluplus®, Sodium lauryl sulphate, Bovine serum albumin, Urea from BASF India Ltd. India ; Acetic acid, Hydrochloric acid, Lactic acid, Glycerol, Methanol, Ethanol from Loba Chemie, India. All chemicals used were of analytical grade.

2.2 Methods:

2.2.1 Formulation of mucoadhesive vaginal films:
Solvent casting method was used for making films. Several polymers such as hydroxyl propyl cellulose and sodium alginate, HPMC E15, Hydroxypropyl cellulose (HPC; MW,140,000), Carrageen and hydroxyethyl cellulose (HEC), polyethylene glycol 400 (PEG 400), Hydroxypropyl methylcellulose CP 50, Hydroxypropylmethyl cellulose—Methocel® K100M, HPMC metolose 90, HPMC K4M, Eudragit L100, Eudragit RL 100, Eudragit RS 100, Kollisolv® PEG-400, tributyl citrate were screened. The trials were taken at 2:1 concentration ratio[9]. Polymers were selected based on parameters such as physical appearance, pealability, thickness and disintegration time of films.

Solvent system used was methanol: ethanol: distilled water. Polymers were weighed and mixed with solvent system using magnetic stirrer at 400 rpm (Table 1). Plasticizers (PEG 400 or propylene glycol) were added and mixing was continued for another 45 minutes. The resultant solution was casted as films on plain surface, dried at 45^{o}C for 15 hrs.

Table 1
Formulation table for plain mucoadhesive film.

Formulation	Polymer 1 (2%)	Polymer 2 (1%)	PEG 400	Propylene Glycol
PF1	Hydroxypropyl cellulose	Sodium alginate	30%	
PF2	Hydroxypropyl methyl cellulose E15	Sodium alginate		30%
PF3	Hydroxyethyl cellulose	carrageen	-	30%
PF4	Hydroxypropylmethyl cellulose CP 50	Sodium alginate	30%	-
PF5	Hydroxypropylmethyl cellulose-methocel ® K 100 M	Zein	30%	-
PF6	HPMC CP 50	Ethyl cellulose	30%	
PF7	Hydroxy propyl methyl cellulose metolose 90	Eudragit L-100	-	30%
PF8	HPMC K4M	Ethyl cellulose		30%
PF9	Hydroxy propyl methyl cellulose metolose 90	Eudragit RS-100	30%	-
PF10	HPMC CP50	Eudragit RS-100	30%	-

Based on preliminary polymer screening polymers HPMC CP50 and Eudragit RS-100 were selected for further study.

2.2.2 Drug Excipient compatibility studies:

Drug excipients compatibility studies were performed considering physical observation and Fourier transform infrared (FTIR) spectroscopy (IRAffinity- 1 FTIR spectrophotometer by Shimadzu). During former studies, blend of the drug and the excipients in suitable ratios (Table 2) were filled in glass vials closed with the rubber stoppers and kept at 40°C/75% RH for the duration of 1 month. The vials were observed for any physical change. And in later examination, compatibility study for ITR was carried out with formulation excipients to determine the possibility of any drug-excipient interactions or incompatibilities. Individual IR spectra of the drug, excipients and mixture of drug and excipients mixed together were taken initially on 1st and then on 30th day respectively.

Table 2
Samples analyzed for drug excipient compatibility studies

Sample	Ratio	Storage condition	Time (In days)
ITR: HPMC CP 50	1:1	25°C/60% RH	Up to 30 Days
ITR: Eudragit RS 100	1:1	and	
ITR: Soluplus	1:1	40°C/75% RH	
ITR: PEG 400	1:1		

2.2.3 Formulation of mucoadhesive film

Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, having large number of hydroxyl groups. It was used as a solubilizer for ITR in 1:1 ratio for preparing polymeric solution.

Solvent casting method was used. Polymeric solution was obtained by dissolving polymers in solvent system. (Table 3). Then itraconazole and soluplus was added in it. Sufficient amount of proportionate dose of ITR was added so that 25 mg per unit of formulation was achieved[8]. Plasticizers (PEG 400 or propylene glycol) were added and mixing was continued. The resultant solution was casted as films on plain surface, dried at 45^{o}C for 15 hrs.

Table 3
Formulation of different batches of drug loaded mucoadhesive vaginal film

Ingredients	ITF 1	IT 2	ITF 3	ITF 4	ITF 5	ITF 6	ITF 7	ITF 8
HPMC CP 50 (%)	1	1.5	2	2.5	1	1.5	2	2.5
Eudragit RS 100 (%)	1	1	1	1	1	1	1	1
PEG 400 (% of dry polymer wt)	30	30	30	30	-	-	-	-
Propylene glycol	-	-	-	-	30	30	30	30
Itraconazole (mg)/ 4 cm^2	25	25	25	25	25	25	25	25
Soluplus ® (mg)/ 4 cm^2	25	25	25	25	25	25	25	25

2.2.4 Characterization and evaluation of mucoadhesive vaginal Films:

a- Physical appearance:

All the prepared vaginal films were visually inspected for colour, clarity, flexibility, and smoothness

b- Thickness:

The thickness of the drug-loaded films was measured by using a screw gauge micrometer at five different points on the patches[9].

c- Uniformity of weight:

The films were subjected to a weight variation test by weighing all the films on a digital weighing machine[2].

d- Folding endurance:

The folding endurance was measured manually by repeatedly folding a small strip of the film (2 × 2 cm) at the same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance[1].

e- Disintegration time of films:

The disintegration time was measured by putting (2 × 2 cm) film in 10 ml of media until it broke[10].

f- Drug content determination:

Pieces of 2 × 2 cm were cut from the formulation and put in 100 ml of methanol. The contents were placed in an ultrasonication bath for one hour. The solution was then filtered through whatman filter paper (0.45 µ) and diluted suitably with methanol. The solution was then analyzed for its absorbance at 261.4 nm using methanol as blank. From the absorbance values, the drug content was determined

$$\% \text{ Drug content} = \left(\frac{\text{Amount of drug recovered}}{\text{Amount of drug added}} \right) *100$$

g- In vitro drug release - Diffusion studies

Franz diffusion cell was used for the in vitro characterization of vaginal film formulations. The fabricated films were placed on the pretreated cellophane membrane and attached to the Franz diffusion cell such that the cell's drug releasing surface towards the receptor compartment was filled with 20 ml of phosphate buffer pH 4.5: methanol (6:4) at 37 ± 0.5°C. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.5°C. Samples (2.0 ml aliquots) were then withdrawn at suitable time intervals (0, 0.5, 1, 2, 3, 4, 5, 6,7,8 and 24 h) and replenished with an amount of medium to maintain the receptor phase volume to 20 ml. The samples were analyzed spectrophotometrically at 261.4 nm[9].

h- In vitro drug release – Dissolution studies

Modified Dissolution technique used for in vitro dissolution study by using shaker incubator, using 80 ml simulated vaginal fluid with 1% SLS media. 25mg /4cm^2 ITR loaded films were used for at 37°C at 20 rpm. 2 ml aliquots were drawn at time point: 1, 2, 3, 4, 5, 6, 7, 8, 24 hrs. the aliquots were analyzed at maximum wavelength 261.4 nm.

i- In –vitro antifungal study:

Antifungal activity was determined using disk diffusion method and determination of minimum inhibitory activity using REMA method in triplicates.

S1 (ITF 7) and S2 (ITF 3) samples were used. Marketed vaginal cream was used as positive control. Candida albicans culture was procured. Sample S1 and S2 were used as per protocol for antifungal activity. For minimum inhibitory concentration determination, 100mg/ml stock of itraconazole was prepared using methanol.

- The test organism was grown in Sabouraud dextrose broth providing incubation period of 24h and then used for the study.
- The optical density of the culture was adjusted using 0.5 McFarland standard (106 cfu/mL). The cell suspension was mixed to homogeneity to give a final density of 1 x 105 CFU/ml and then taken ahead for checking the antifungal activity using agar cup diffusion method.
- Each plate contained four samples- a positive control, a negative control (St. D/w) and 2 test samples. Sample containing discs were placed onto the culture containing plate and the plate was incubated at room temperature for 24h.

f- Tensile Strength Analysis
TA.TXT plus Texture Analyser (Stable Micro Systems, Surrey, UK) was used to study mucoadhesion and tensile strength of film. The equipment was used in compression mode loaded with a 5 mm circular head probe in order to puncture a film secured in perpendicular position at a speed of 0.5 mm/s. The force and distance registered at film breakage were considered as the burst strength (resistance to fracture) and elasticity (deformability)[11].

g- Stability study as per ICH guidelines:
The films were covered with aluminum foil and placed in polybag for the study, as per ICH guidelines at 40 ± 2 ^{o} C/ 75 ± 5% RH for accelerated study and 25 ± 2 ^{o} C/ 60 ± 5% RH for long term stability study. The samples were evaluated for any changes in visual appearance, assay and in-vitro release profile after one month of storage.

RESULTS AND DISCUSSIONS:

3.1 Formulation of vaginal mucoadhesive films:

The preparation is meant to prolong the residence time at the site of infection so that it can deliver the drug for longer duration with sustained release pattern, while ensuring minimum effective concentration. Thus, both drug control release and swelling capability play an important key role. Molecular weight, hydrophilicity and chemical structure of polymers dramatically influence the properties of film, such as mucoadhesion, disintegration time and mechanical strength. So, different combination of polymers was analyzed to make mucoadhesive films and then the drug was loaded in optimum batch. Ten formulation

batches were prepared, considering different polymer combinations, suing two different plasticizers (polyethylene glycol and propylene glycol). These preliminary batches were evaluated for physical appearance, peelabilty, film thickness and disintegration time.

Amongst ten formulation batches, PTF 1, PTF 4, PTF 5, PT 7 were not peelable. In this part of study, ITR was not incorporated. This work evaluated different combinations of polymers and effect of plasticizer. The parameters of remaining batches are shown in Table 4.

Table 4
Results of characterization of films with different polymer combinations

Parameter Batches	Physical appearance of films	Thickness of films (mm) (n = 3)	Disintegration Time (n = 6)	Peelability of film	Swelling Index
PTF 2	Sticky	0.22 ± 0.56	10 ± 0.26 min	Peelable	22.8 ± 2.56
PTF 3	Hazy	0.14 ± 0.27	8 ± 0.55 min	peelable	31.5 ± 0.45
PTF 6	Hazy, sticky	0.15 ± 0.43	30 ± min	Peelable	40.8 ± 0.66
PTF 8	Slightly clear, sticky	0.12 ± 0.77	40 ± min	Peelable	17.2 ± 0.39
PTF 9	Slightly Hazy	0.28 ± 0.22	4 ± hrs	Peelable	32.1 ± 0.58
PTF 10	Clear, Soft	0.20 ± 0.48	23 ± hrs	Peelable	45.9 ± 0.10

Amongst all batches, PTF 10 gives a clear and soft film of 0.22 mm thickness, with disintegration time of 23 hrs. So, it was concluded that polymeric solution of HPMC CP 50 and Eudragit RS 100 should be used for further study. Considering this, drug excipient compatibility studies were conducted.

Drug excipients compatibility studies were performed between ITR: HPMC CP 50, ITR: Eudragit RS 100, ITR: Soluplus, ITR: PEG 400. It was conducting considering physical observation and Fourier transform infrared (FTIR) spectroscopy. No change was observed in physical mixtures in visual appearance on 30th day of study. FTIR spectra of ITR on scale of 4000 – 400 cm^{-1} confirmed identity of drug. Peaks corresponding to wavenumbers 1520 corresponds to C = C stretching (Aromatic), 3739 to C-H stretching (Aromatic), 2931 to C-H stretching (Alkyl), 1653 to C = O stretching (Ketone), 1220 to C-N stretching (Triazole), 1568 to N = N = N stretching (Triazole), 3446 to N-H stretching (Amino). FTIR spectra of ITR: Eudragid RS 100, ITR: Soluplus, ITR: HPMC CP 50 also indicate that there is no interaction between drug and polymers (Fig. 1).

3.2 Characterization of drug loaded films:

To optimize the proportion of these polymers, eight trial batches were run by varying the proportion of these two polymers and type of plasticizer (Table 3). The evaluation parameters folding endurance, disintegration time and percent drug release were determined. Plasticizer is introduced in formulation to increase distance and intermolecular interactions with polymer molecules[12]. Thus, the type and amount of plasticizer, in turn, governs the quality and mechanical strength of mucoadhesive film. As we increase the quantity of plasticizer, the folding endurance increases as the film becomes better plasticized and thus not easily deformed. However, if plasticizer choice is not correct or if it is added in high quantity, it may lead to over- plasticizing that is indicated by rubbery state of film, thus the continuity of film may be comprimized[13]. Thus, the mechanical properties of film were optimized at this stage with effective drug release. It was observed that drug release was more than 90% in ITF 3, ITF 6 and ITF 7, which is highest from ITF 3, approaching 100%, whereas the folding endurance was more than 250 from ITF 1, ITF 3, ITF 4 and ITF 5, which highest value of 350 for ITF 3. Thus, ITF 3 is said to be optimized formulation. Figure 2 ensures that ITF 3 gives the optimum results and should be used for drug loading (Table 5).

Table 5
Optimized drug loaded film batch

Ingredients	**Quantity/4cm^2**
ITR	25 mg
HPMC cp 50	300mg
Eudragit RS 100	150 mg
PEG 400	135 mg
SOLUPLUS	25 g

Table 6 enumerates the evaluation parameters of the drug loaded vaginal film.

Table 6
Results for optimized batch

Test	**Results**
Thickness (mm)	0.18 ± 0.53
Weight uniformity	150 ± 0.27
Folding endurance	351 ± 0.88
Disintegration Time	20 ± 0.67 hrs
Drug content	99.5 ± 0.98%
Diffusion/Dissolution	Preliminary experiments undertaken

The minimum inhibitory concentration (MIC) of the samples against the test organism was determined by using resazurin microtitre plate assay. This assay was performed using flat bottom 96-well clear microtiter plates. The wells in first row of each column were filled with 100 µl of sabouraud dextrose broth with standard antibiotics while second row of each column was filled with 100 µl media. The third row was filled with 100 µl 2X media and 100 µl of samples. Then fourth row onwards, each well was filled with 1X Media (sabouraud dextrose broth). An identical two-fold serial dilution was made from 3rd row to the 12th row. Lastly, in all the wells 10 µl of culture were added and mixed thoroughly. A final concentration of 3rd row to 12th row was ranging from 50% dilutions to 0.1% dilution (Concentration changes according to sample concentration) with 1 x 105 CFU/ml. The cultured microplate was sealed with the lid and incubated at room temperature for 24h. The MIC of samples was detected following addition (5µL) of 2mg/mL Resazurin in all the wells and incubated at 37°C for 30 min. Microbial growth was determined by observing the change of color of Resazurin in the micro plate wells (pinkish-red formazan when there is growth and blue when there is no growth). MIC was defined as the lowest sample concentration showing no color change (clear) and exhibited complete inhibition of microbial growth. This study was carried out in triplicates.

The samples displayed antifungal activity against the test organisms. REMA assay was performed for ITR sample and it show MIC at 6.25mg/ml concentration against test organism (Fig. 3, Table 7).

Table 7
Results for Antifungal activity

	Zone of inhibition in mm			
Organisms	S1	S2	P.C.	N.C.
Candida albicans	20	19	15	-

The tensile strength, puncture strength and adhesive strength were observed to be 10585.9 g, 2200.47 gm and 0.81 gm respectively. Puncture strength was strongly correlated with tensile strength and could be used to obtain necessary information about the mechanical characteristics of films (Fig. 4).

Stability studies indicate that the batches from both the storage conditions did not show any colour change. No effect of temperature or humidity could be visually observed. The drug content after assay was found to be 96.15% after 30 days, as compared to 97.17% on day 1 at 40°C ± 2°C /75% RH ± 5% RH. It was observed to be 96.71% after 30 days, as compared to 97.17% on day 1 at 25°C ± 2°C /60% RH ± 5% RH.

CONCLUSION

Sufficient dose of ITR could be incorporated in the mucoadhesive vaginal film formulation having uniform drug distribution. HPMC cp 50, Eudragit RS 100, PEG400, Propylene glycol, Soluplus® excipients were used for effective formulation of vaginal films. Various evaluation tests were performed also in

vitro antifungal study and in vitro dissolution study had been done. Vaginal administration allows self-administration with minimal professional interference. Further, intra-vaginal drug delivery ensures site-specific drug delivery, greatly improves the therapeutic efficacy of drugs. Apart from these advantages, vaginal delivery also offers a promising alternative for systemic drug bioavailability by avoiding first-pass metabolism. Mucosal sites due to their easy accessibility, the low enzymatic activity allows easy removal of the carriers, thereby offering an attractive non-invasive alternative for rapid, controlled drug delivery.

Declarations

Declaration of Competing Interest

The authors report no declarations of interest.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent

Not applicable.

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Author Contribution

Author contributionsS.D under the supervision of Dr GS contributed to the conception and design of the study. Material preparation, data collection and analysis were performed by S.D, J.S and Dr N C. The first draft of the manuscript was written by S.D and J. S. S.D and J.S prepared the figures. All authors read and approved the final manuscript.

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Data availability statement

The authors declare that they have no competing interests

References

1. Nematpour N, Moradipour P, Zangeneh MM, Arkan E, Abdoli M, Behbood L (2020) The application of nanomaterial science in the formulation a novel antibiotic: Assessment of the antifungal properties of mucoadhesive clotrimazole loaded nanofiber versus vaginal films. Mater Sci Eng C Mater Biol Appl. https://doi.org/10.1016/J.MSEC.2020.110635
2. Farhan MA, Moharram AM, Salah T, Shaaban OM (2019) Types of yeasts that cause vulvovaginal candidiasis in chronic users of corticosteroids. Med Mycol 57:681–687
3. Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R (2018) Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Infect Dis 18:e339–e347
4. Li J, Regev G, Patel SK, Patton D, Sweeney Y, Graebing P, Grab S, Wang L, Sant V, Rohan LC (2019) Rational Design of a Multipurpose Bioadhesive Vaginal Film for Co-Delivery of Dapivirine and Levonorgestrel. Pharmaceutics 2020, Vol 12, Page 1 12:1
5. Hussain A, Ahsan F (2005) The vagina as a route for systemic drug delivery. J Control Release 103:301–313
6. Notario-Pérez F, Cazorla-Luna R, Martín-Illana A, Galante J, Ruiz-Caro R, das Neves J, Veiga MD (2020) Design, fabrication and characterisation of drug-loaded vaginal films: State-of-the-art. J Control Release 327:477–499
7. Yin X, Daintree LS, Ding S, Ledger DM, Wang B, Zhao W, Qi J, Wu W (2015) Itraconazole solid dispersion prepared by a supercritical fluid technique: preparation, in vitro characterization, and bioavailability in beagle dogs. Drug Des Devel Ther 9:2801–2810
8. Xia M, Liu Y, Chen J, Xu R, Dai G (2024) The Pharmacokinetic Interaction of Tirabrutinib with Voriconazole, Itraconazole, and Fluconazole in SD Rats by UPLC-MS/MS. https://doi.org/10.2174/0109298673268883231108062655. Curr Med Chem
9. Dolci LS, Albertini B, Di Filippo MF, Bonvicini F, Passerini N, Panzavolta S (2020) Development and in vitro evaluation of mucoadhesive gelatin films for the vaginal delivery of econazole. Int J Pharm. https://doi.org/10.1016/J.IJPHARM.2020.119979
10. Akil A, Parniak MA, Dezzutti CS, Moncla BJ, Cost MR, Li M, Rohan LC (2011) Development and characterization of a vaginal film containing dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), for prevention of HIV-1 sexual transmission. Drug Deliv Transl Res 1:209–222
11. Dobaria N, Mashru R (2010) Design and in vitro evaluation of a novel bioadhesive vaginal drug delivery system for clindamycin phosphate. Pharm Dev Technol 15:405–414
12. Sakata Y, Yamaguchi H (2011) Effects of calcium salts on thermal characteristics of hydroxypropyl methylcellulose films. J Non Cryst Solids 357:1279–1284
13. Calvo NL, Svetaz LA, Alvarez VA, Quiroga AD, Lamas MC, Leonardi D (2019) Chitosan-hydroxypropyl methylcellulose tioconazole films: A promising alternative dosage form for the treatment of vaginal candidiasis. Int J Pharm 556:181–191

Figures

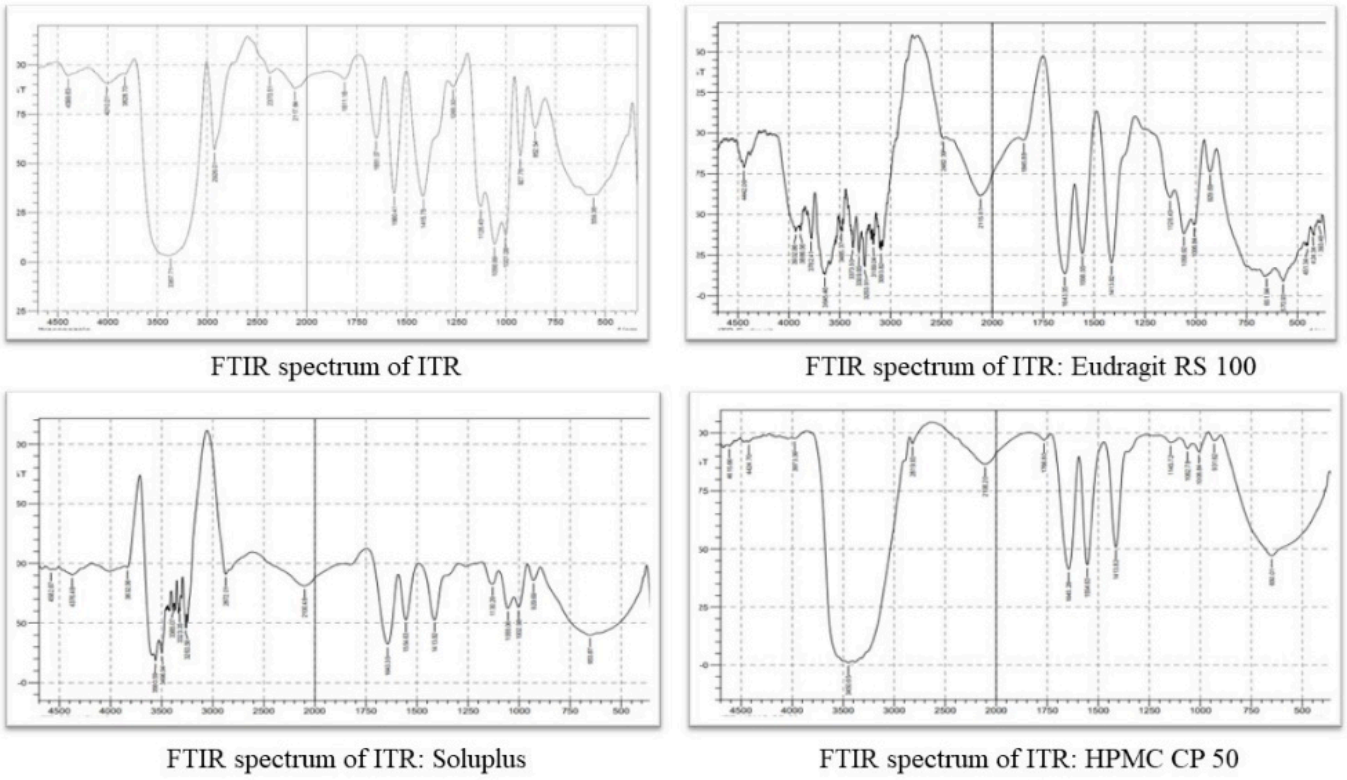


Figure 1

FTIR Spectra

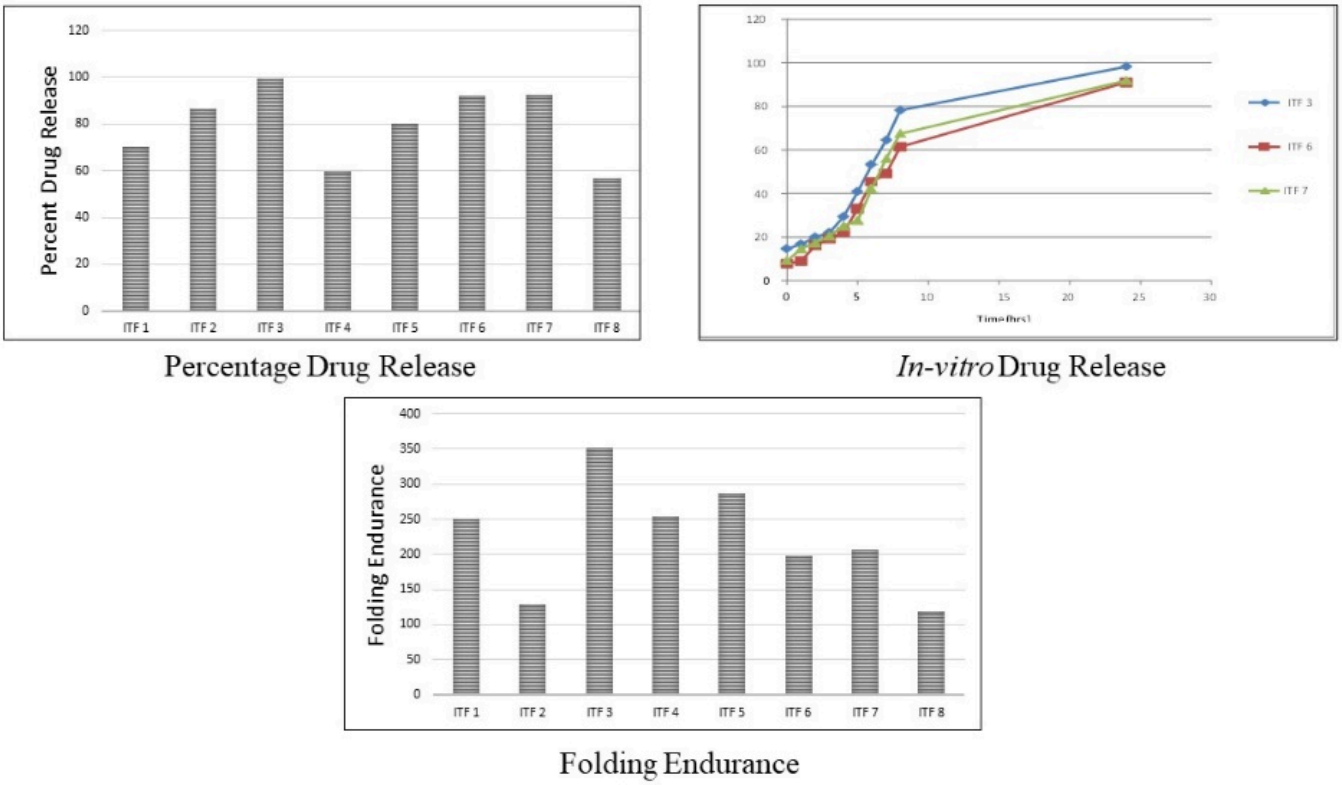


Figure 2

Characterization of drug loaded films for optimizing formulation table

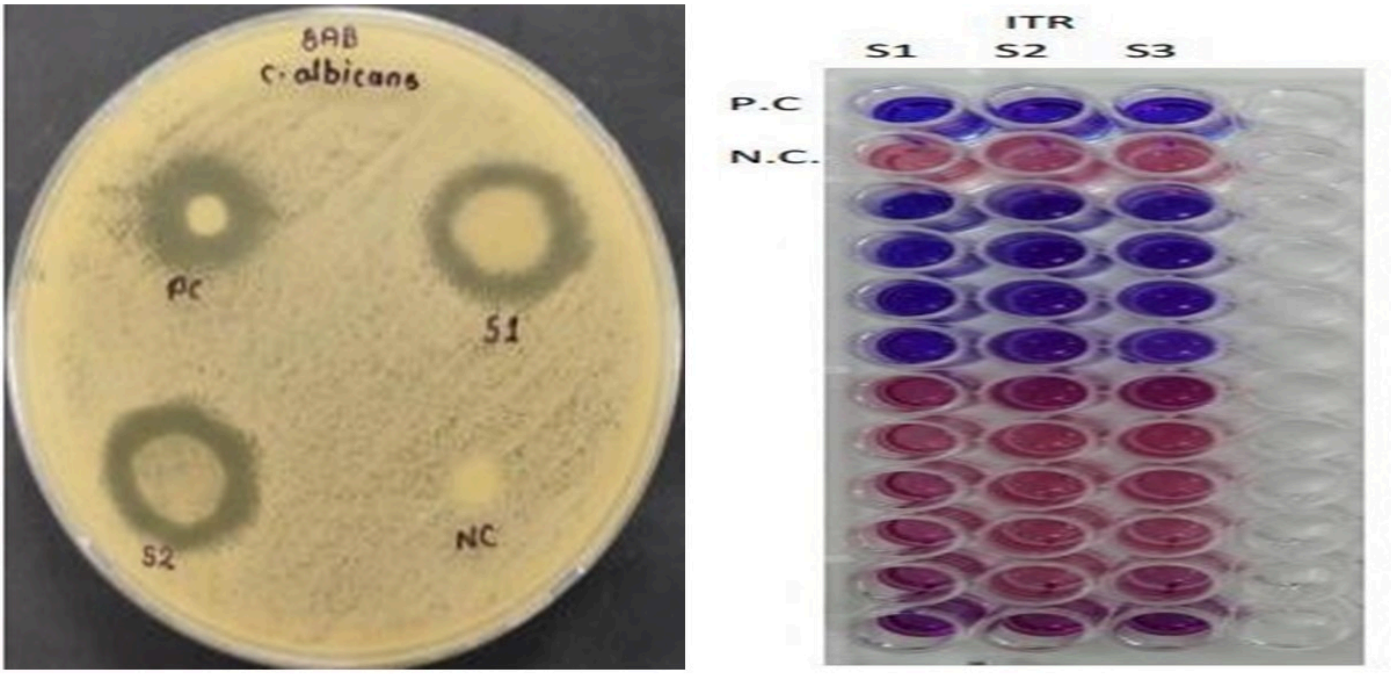
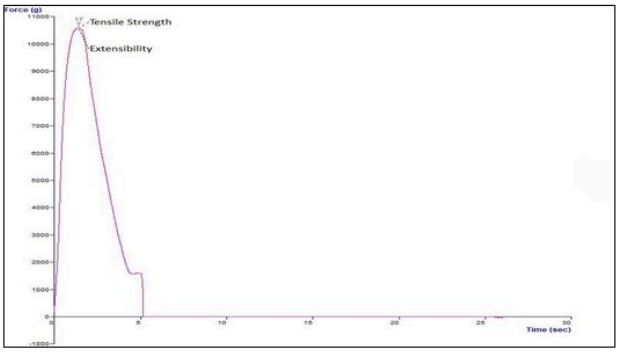
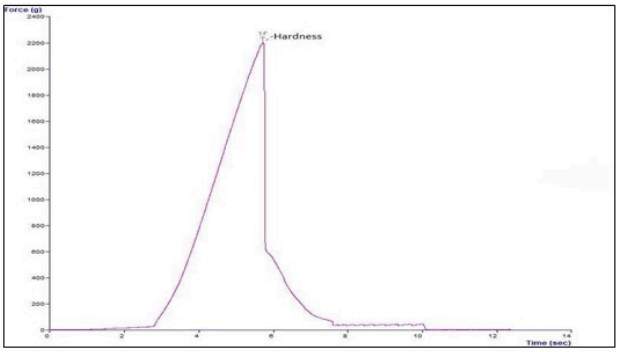


Figure 3

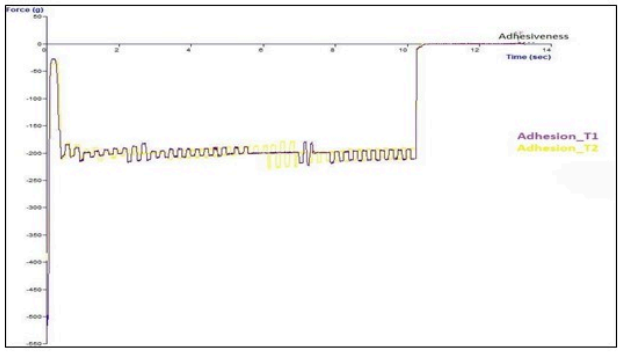
Results for Antifungal activity and Minimum Inhibitory Concentration



Determination of tensile strength



Determination of penetration strength



Determination of adhesive strength

Figure 4

Texture analysis of film