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Luliconazole Loaded Electrospun Mucoadhesive Nanofiber: A Novel Nanoconstruct For The Treatment Of Vulvovaginal Candidiasis

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Abstract
Vulvovaginal candidiasis primarily caused by the overgrowth of Candida albicans affecting women mainly in their reproductive ages. Main challenge is delivering the drug to the desirable site. Vagina is an intricate route for drug delivery due to hormonal activity, presence of microbiota and enzymes, change in pH, excessive secretion of vaginal fluid, and thickness of the vaginal tissue layer that catalyses with age, which alters the absorption and bioavailability of the drug. Conventional dosage forms exhibit poor biodistribution, limited effectiveness, undesirable effects, chemical degradation, clearance and lack of selectivity. To overcome the aforesaid challenges, necessitates a strategic formulation with improved therapeutic outcomes for eliminating and countering the recurrence of the disease. Therefore, developing a novel system is required for localized drug delivery with a prolonged release in a single dose, enhanced fibre adhesion, retention, and drug penetration to the vaginal mucosa. Nanofiber is the new biomedical application of nanotechnology used as a carrier for effective drug delivery and have a diameter in the order of a few nanometres to over 1 μm (more typically 50˜500 nm) and possess unique characteristics, such as: extraordinary high surface area per unit mass, sustained release, enhanced solubility, high drug loading capacity, flexibility, and mechanical properties which make them a better tool to overcome the constraints of vaginal drug delivery carriers in VVC management. In this study, polycaprolactone, gelatine, tea tree oil and luliconazole drug was used for the fabrication of nanofiber. Nanofibers produced and optimized in this research work was characterized by SEM, FTIR, DSC, XRD, swelling study, drug uniformity, entrapment efficiency, contact angle, mucoadhesive test, and mechanical strength. In vitro drug release, drug permeation study, vaginal irritation test and anti-candidal activity were also performed. SEM analysis showed the uniform and less bead-free PCL/gelatine fibres. FTIR proved that there is no interaction between drug and excipients. DSC indicates the absence of characteristic peak of the luliconazole drug in the nanofiber revealed the LCZ was amorphous by the loading of LCZ in the nanofiber. In the swelling study, maximum increment in the swelling was obtained at 4hr. The entrapment efficiency of drug loaded nanofiber was found to be 89.2 ± 0.8 %. The contact angles of blank nanofiber, nanofiber with tea tree oil and LCZ-loaded nanofiber was found to be 46.5, 62.95 and 65.78 respectively. The mucoadhesive force of blank nanofiber, TT oil-loaded nanofiber, and LCZ-loaded nanofiber was obtained as 1000 dynes, 400 dynes, and 300 dynes respectively. The mechanical strength of blank nanofiber, TT oil-loaded fiber, and drug-loaded nanofiber was 0.187 N/mm, 0.148 N/mm, and 0.445 N/m. The release reached 67.7 ± 3.4 % after 48 hours of study which was found more than the release of drug from the suspension and drug release through nanofiber was best addressed by the Korsmeyer-Peppas model. The percentage cumulative drug permeation was found as 54.13 ± 0.32 % within 6 hours for drug with oil loaded nanofiber, 50.43 ± 0.84 % for only drug loaded nanofiber and 31.87 ± 1.13 % for suspension. The zone of inhibition (ZOI) of luliconazole-loaded nanofiber was 12.8 ± 0.53 mm after 48 hours. Thus, the luliconazole loaded nanofiber fabricated for the first time which successfully could work in the anticandidal action for the management of vaginal candidiasis.
Keywords: *Vulvovaginal, Polycaprolacton, Nanofiber and Luliconazole*

INTRODUCTION:

Vulvovaginal candidiasis, commonly known as a yeast infection, is a fungal infection that affects the vulva and vagina (de Cássia et al., 2021). It is primarily caused by the overgrowth of Candida albicans, a type of yeast that is normally present in the vagina in small amounts and responsible for 90-95% of the infection and the rest by non albicans species such as C.glabrata, C.krusei, C.parapsilosis, and C.tropicalis (Martins N et al.,2014). Vulvovaginal candidiasis is a prevalent fungal infection affecting women of all ages and caused primarily by the overgrowth of Candida albicans, a yeast that naturally resides in the vaginal microbiota, this condition leads to a range of uncomfortable symptoms (Willems HM et al.,2020). Despite being a common ailment, Vulvovaginal candidiasis can significantly impact a person's quality of life. Understanding its causes, symptoms, and treatment options is crucial for effective management and prevention (Adolfsson A et al.,2017). Vulvovaginal candidiasis (VVC) is a widespread condition, with epidemiological data indicating its prevalence varies across different populations and regions (Maraki S et al.,2017). Globally, it affects millions of women annually estimated up to 75% of women will experience at least one episode of VVC during their lifetime, with around 5-8% experiencing recurrent infections (Gonçalves B et al.,2016). VVC can occur at any age, it is most commonly diagnosed during the reproductive years, with peak incidence typically observed in women aged 20 to 40 years old (Salvi M 2019). However, it can also affect prepubescent girls and postmenopausal women. Several factors can increase the risk of developing VVC, including pregnancy, diabetes mellitus, use of oral contraceptives, antibiotic use, immunosuppression, hormonal fluctuations during the menstrual cycle, and sexual activity (Disha T et al.,2022). Recurrent VVC, defined as four or more episodes within a year, affects a subset of women and can be particularly challenging to manage (Lema VM 2017). Recurrences may be due to persistent colonization of Candida species in the vaginal microbiota, host immune factors, or other predisposing conditions. The prevalence of VVC can vary geographically, with higher rates reported in certain regions. Factors such as climate, hygiene practices, socioeconomic status, and access to healthcare may contribute to these variations. VVC can cause significant discomfort, including itching, burning, and pain, leading to impaired quality of life (Rosati D et al.,2020). Recurrent episodes may also result in psychological distress and frustration for affected individuals. The epidemiology of VVC is essential for healthcare providers to effectively diagnose, treat, and prevent this common gynecological condition. Additionally, ongoing research into risk factors and prevention strategies is crucial for improving outcomes and reducing the burden of VVC on affected individuals and healthcare systems.

Nanofibers:

Nanofibers have emerged as novel nanotech applications designed for drug delivery, tissue healing, wound dressing, and implants after surgery with numerous advantages (Elsadek NE et al.,2022). Therefore, developing a novel system is required for localized drug delivery with a prolonged release in a single dose, enhanced fiber adhesion, retention, and drug penetration to the vaginal mucosa. Nanofibers are a specific type of nanoformulation that has shown great promise in the treatment of Vulvovaginal Candidiasis (VVC). They are ultrafine fibers with diameters in the nanometer range, typically produced through electrospinning (Vanić Ž et al.,2021).

Applications of nanofibers:

Nanofibers as formulations have a wide range of applications across various fields due to their unique properties such as high surface area-to-volume ratio, tunable porosity, and the ability to incorporate multiple functionalities (Hiwrale A et al.,2023).

1. **Drug Delivery**

   Nanofibers can encapsulate drugs and provide a controlled release over time, improving therapeutic efficacy and patient compliance. Drugs can be physically embedded within or chemically conjugated to the nanofibers. Functionalized nanofibers can target specific tissues or cells, enhancing the precision of drug delivery and minimizing side effects. Nanofibers can carry multiple drugs, allowing for combination therapy, which is particularly useful in treating complex diseases like cancer (Singh A et al.,2018).

2. **Tissue Engineering**
   Nanofibers mimic the extracellular matrix, providing a conducive environment for cell attachment, proliferation, and differentiation. They are used to create scaffolds for regenerating skin, bone, cartilage, and other tissues. Nanofiber scaffolds can deliver and support stem cells, enhancing their survival and differentiation into the desired tissue types (Sell S et al.,2007).
3. **Wound Healing**
   Nanofiber mats can be used as wound dressings due to their high absorbency, breathability, and ability to provide a moist environment, which promotes faster healing. They can also be loaded with antimicrobial agents to prevent infections. Nanofiber dressings can protect burn wounds, provide pain relief, and release therapeutic agents to promote healing (Liu X et al.,2021).
4. **Biomedical Implants**
   Nanofibers can be used to coat biomedical implants, enhancing their integration with surrounding tissues and reducing the risk of rejection. Nanofiber coatings on stents can release drugs to prevent restenosis (re-narrowing of blood vessels) after implantation (Leung V et al.,2011).
5. **Filtration**
   Nanofibers' high surface area and tunable pore sizes make them ideal for capturing pollutants, pathogens, and particulates in air and water filtration systems. Nanofibers can be incorporated into protective clothing to filter out harmful substances, providing enhanced protection in hazardous environments (Qin X et al.,2017).
6. **Cosmetics**
   Nanofibers can be used in cosmetic formulations to deliver active ingredients such as vitamins, antioxidants, and moisturizing agents more effectively to the skin. Nanofiber layers in face masks can provide enhanced filtration of pollutants and pathogens while allowing breathability (Yilmaz F et al.,2016).
7. **Food Industry**
   Nanofibers can be used in active food packaging to extend shelf life by incorporating antimicrobial agents or oxygen scavengers. Nanofibers can be used to encapsulate Flavors, nutrients, or probiotics, providing controlled release in food products (Noruzi M et al.,2016).

Physico-chemical characterization & identification:

The drug sample was analyzed for the organoleptic properties and physicochemical parameters such as appearance, color, odor, melting point, solubility in different solvents. UV spectrophotometric study and FT-IR analysis were also performed.

1. **Organoleptic properties:**

The sample of luliconazole drug was characterized for its physical properties such as color, physical state, and odor.

2. **Determination of solubility:**

Solubility of luliconazole was checked in the water, methanol, Ethanol, dichloromethane, chloroform, Dimethyl formamide and SVF pH 4.5. With shake flask method, the solubility studies were performed and, in this technique, 20-30 ml of different solvents as mentioned earlier with excess amount of drug was taken in different flasks. Flasks were positioned on the mechanical shaker after adding drugs to all the flasks. Apposite samples were withdrawn, filtered and lastly set aside for analysis by Shimadzu UV-spectrophotometer (Prakash K et al.,2008).

Water	0.47 ± 0.02 mg/ml	Very slightly soluble
Methanol	34.4 ± 0.12 mg/ml	Soluble
Ethanol	32.12 ± 0.13 mg/ml	Soluble

DCM	26.43 ± 0.22 mg/ml	Sparingly soluble
Chloroform	17.21 ± 0.29 mg/ml	Sparingly soluble
DMF	33.20 ± 0.18 mg/ml	Soluble
SVF pH 4.5	1.78 ± 0.14 mg/ml	Slightly soluble

3. **Preparation of calibration curve of luliconazole in methanol and SVF(pH 4.5):**

Calibration curve of luliconazole was plotted in methanol and SVF (pH 4.5) by concentration (µg/mL) vs. absorbance at 295 nm and 299nm respectively. These prepared calibration curves were used for routine analysis of drug concentration.

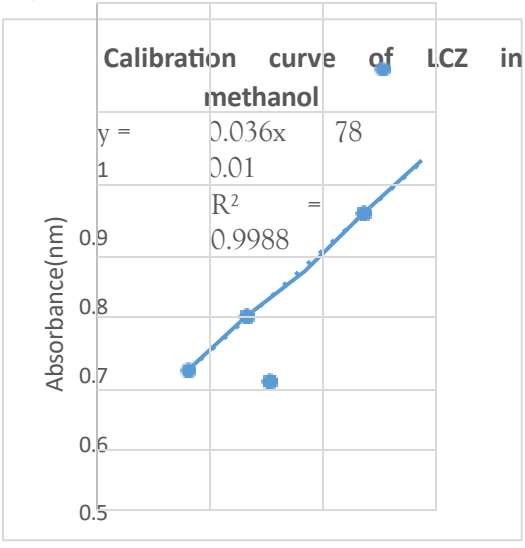
2. **Table-Absorbance of luliconazole in methanol and SVF (pH 4.5)**

Absorbance of luliconazole in methanol at 295 nm		
Concentration (µg/ml)	**Absorbance at λmax 295nm**	**%RSD**
5	0.2±0.001	0.76
10	0.381±0.003	0.92
15	0.541±0.002	0.38
20	0.739±0.001	0.14
25	0.921±0.001	0.11

Absorbance of Luliconazole in Simulated vaginal fluid (pH 4.5) at 299nm		
Concentration (µg/ml)	**Absorbance at λmax 299nm**	**%RSD**
5	0.639±0.001	0.09
10	0.701±0.001	0.16
15	0.732±0.00	0.54
20	0.765±0.002	0.26
25	0.798±0.002	0.25

* RSD- Relative standard deviation

3. **Fig. Calibration curve of Luliconazole in methanol and SVF (pH 4.5**



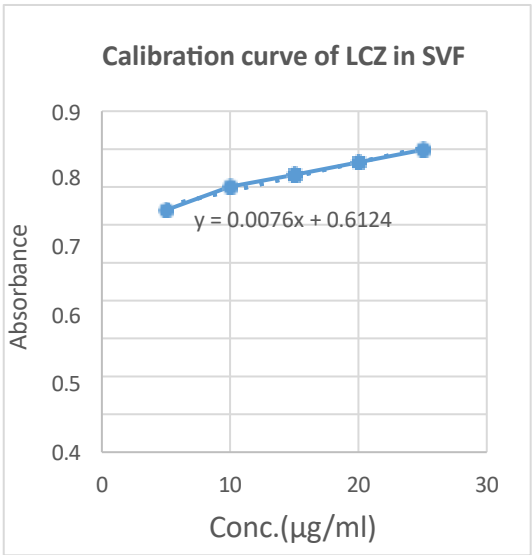


Fig. FTIR spectra of luliconazole

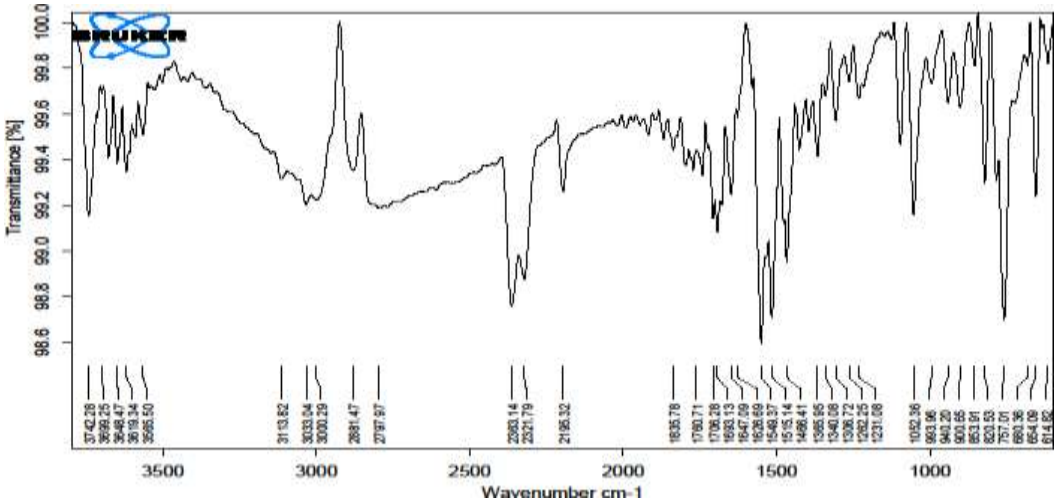
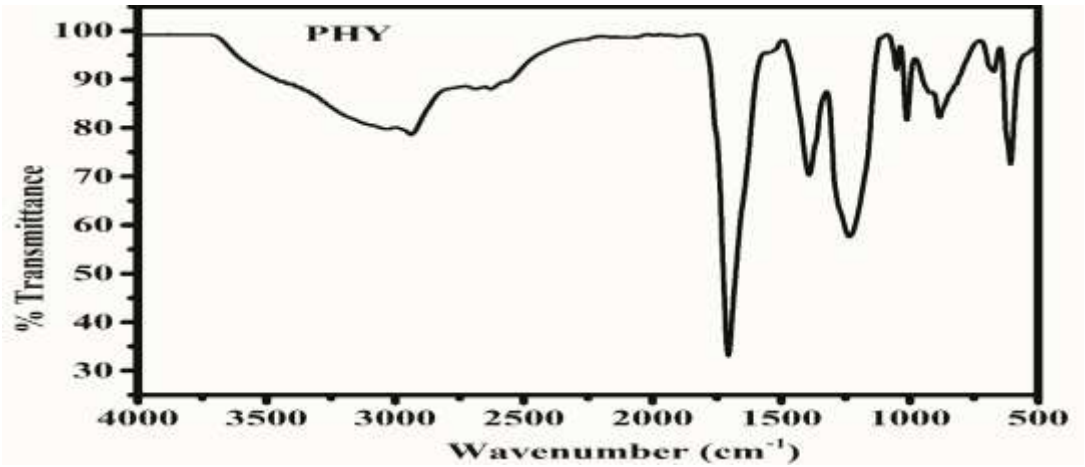


Fig. FTIR spectra of physical mixture



Melting point determination:

The melting point analysis for drug identification was performed by capillary method. Drug powder was filled in the fine glass capillary with the help of spatula. The capillary tube was then connected with the HICON melting point apparatus (Ningbo Hicon Industry Co. Ltd, China) with the regulated thermometer. The temperature point was observed and noted at which the melting takes place (Giordano F et al.,2003). 4.3.4. Partition coefficient by using the Shake flask method, the drug partitioning coefficient was analyzed. The separating funnel used in this process was filled with 50% of n-octanol and rest 50% with water. An excess amount of drug was transferred and then placed on the mechanical shaker. For 48 h conditions of mechanical shaker were maintained at 25°C and 50 rpm. At the end of 24 h, solution was transferred to the separating funnel that is attached to the stand and was permitted to reside intact for next 24 h. Both the solvents were separated by this 48 h process and then the sample was collected, filtered to get the absorbance at the particular λmax using UV spectrophotometer (S Bharate S et al.,2016). By using the following formulae given below the partition coefficient was calculated.

$$Partition\ coefficient = Concentration\ of\ drug\ in\ octanol / Concentration\ of\ drug\ in\ distilled\ water.$$

Solution preparation and fabrication by electrospinning:

Polymeric solutions of PCL: gelatin were produced in three different ratios 50:50, 60:40, and 70:30 in 2% acetic acid solvent and formic acid (3:1) in ratios of 8%,10%, and 12%. Fibers of PCL/Gelatin were fabricated with an electrospinning technique which involved the insertion of polymeric solution in the syringe needle, attached to the pump and voltage generator. The flow rates were 0.3 ml/h, 0.5 ml/h, and

0.7 ml/h and voltages of 16 kV, 18 kV, and 20 kV were considered. The polymeric solution formed a jet when ejected out from the needle and collected on the aluminum foil.

Box Behnken statistical Design for the optimization process:

Box Behnken design was used in this research work to optimize the different parameters to get the minimum mean fiber diameter. For the optimization purpose, four factors and a three-level range (-1, 0, and 1) were designed, including parameters or factors such as PCL polymer concentration, solvent concentration, flow rate, and applied voltage. Three levels that were considered for optimization values are mentioned in table. A total of 29 samples were generated through the BBD using the design-expert® software for further analysis to get the optimized sample.

Table. Experimental factors with their range and levels for optimization of PCL/gelatin nanofibers.

Independent Parameters	Factors	Unit	Range and levels		
			-1	0	1
PCL Concentration	A	% wt	50	60	70
Solvent concentration	B	%	10	12	14
Voltage	C	kV	16	18	20
Flow rate	D	mL/h	0.3	0.5	0.7
Fiber diameter	Y	nm			

Drug Loading in optimized nanofiber:

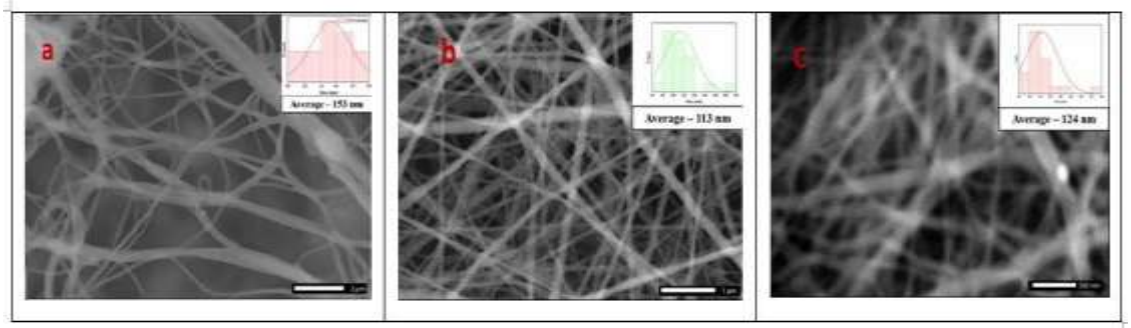
Tea tree oil was taken in different concentrations i.e. 2.5%, 5%, 7.5%, and 10% which were added to the optimum polymer blend for further nanofiber preparation. Concentration at which uniform fiber with minimum diameter formed was selected for further drug loading. The luliconazole drug (5% with respect to the polymeric solution) was mixed in tea tree oil and then added to the polymeric solution. The mixture was stirred for 12 hours at room temperature. The prepared solution was electrospun at different variables considered. Electrospun nanofibers were obtained on aluminum foil and dried at room temperature.

Characterization of optimized electrospun nanofibers:

1. **SEM analysis:**

The morphology and diameter of electrospun nanofibers were examined through SEM (Jeol, japan). A small part of fiber was cut and placed over the sample holder of SEM and then coated with a layer of gold. Images were taken from different positions and the average diameter was calculated through the instrument itself (Gautam S et al.,2013).

4. **Fig.SEM images of (a) PCL/gelatin nanofiber, (b) 7.5% TT oil-loaded fiber, and (c) LCZ-loaded nanofiber**



2. **FTIR Analysis:**

The small pieces of electrospun nanofibers were cut and mixed with KBr to make small pellets. The spectrum was recorded over a range between 400 cm-1 to 4000 cm-1 with a resolution of 2 cm-1. The peaks of drug, excipients, drug-loaded nanofibers were determined.

3. Differential Scanning Calorimetry (DSC) Analysis:

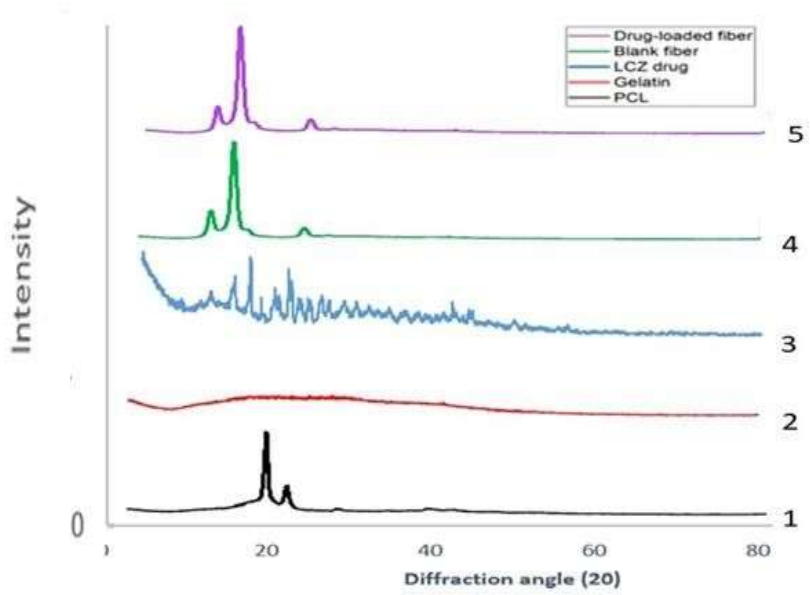
Formulated nanofibers were analyzed for the thermal stability of the drug and polymers used. This study was carried out by weighing 2 mg of the sample placed in a crucible and pressed with a pressing machine. The crucible containing the sample was placed in the DSC instrument and the sample was heated from 20 ^{0}C to 400 ^{0}C temperature with a heating rate of 10 ^{0}C/ min under a nitrogen atmosphere (Tuğcu-Demiröz F et al.,2020).

4. XRD analysis:

Nanofiber samples were scanned at a speed of 2°C/min at room temperature using an X-ray diffractometer. The data were collected from 2θ° = 10° to 2θ° = 80° interval using Rigaku, Japan, SmartLab 9kW instrument.

Fig. XRD pattern of (1) PCL (2) gelatin (3) LCZ drug (4) blank nanofiber

(5) LCZ-loaded nanofiber



5. Degree of swelling:

The three dried nanofiber samples i.e. blank, TT oil-loaded, and LCZ-loaded were cut and weighed. Then these samples were immersed in SVF pH 4.5 at room temperature. Samples were weighed at different time intervals for 6 hours and readings were noted. The degree of swelling was determined by using a formula given in equation (1):

Degree of Swelling (%) = (W-Wd) / Wd * 100

where W is the weight of swollen nanofiber sample and Wd is the weight of the dried nanofiber sample (Zhu X et al.,2015).

6. Entrapment efficiency:

The drug-loaded nanofiber of a known area (1cm x1cm) was cut and dissolved in methanol and SVF (1:1) ratio. The amount of drug in the solution was determined by using UV spectrophotometer (Tuğcu-Demiröz F et al.,2021). The drug entrapment efficiency of the nanofiber was calculated by the following formula:

Entrapment efficiency (%) = Actual amount of drug / Therapeutic amount of drug × 100

7. Drug uniformity of nanofibers:

The drug-loaded nanofiber sample of 1cm* 1cm was dissolved in 10ml of methanol. A total of five samples of nanofiber were taken. Then analysed in HPLC for drug content.

5. **Table. Nanofiber samples showing drug content (%)**

Samples of nanofiber	**Peak Area**	**Drug content (%)**
Sample 1	1230844.9	86.4%
Sample 2	1246515.3	87.5%
Sample 3	1237967.8	86.9%
Sample 4	1215174.4	85.3%
Sample 5	1260761.2	88.5%

Average drug content was found to be 86.92 ± 1.07. Standard deviation is within range.

8. Contact angle:

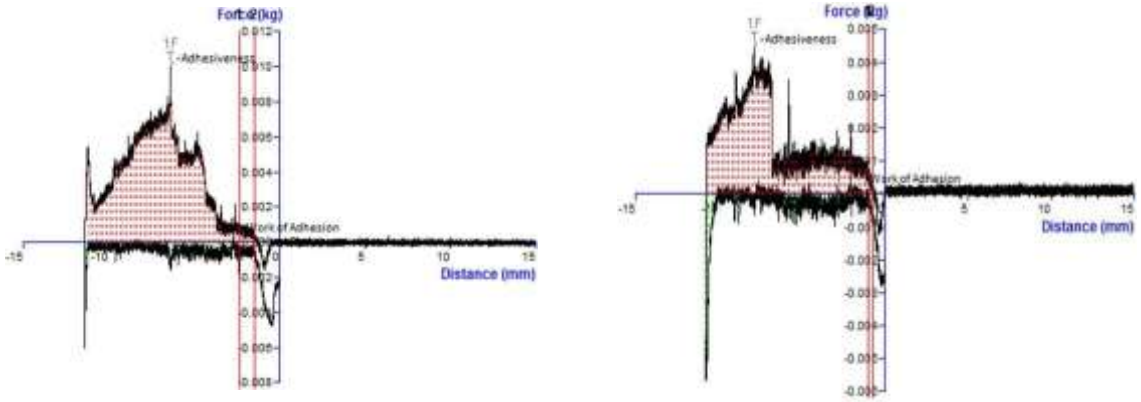
Contact angle measurements were carried out by Dataphysics, Germany, OCAH 230 instrument. Measurements were carried out with SVF on nanofiber samples at room temperature. The sessile drop volume was maintained as 5µl in all samples using a microsyringe. Contact angles were measured with definite time intervals for a single drop and the measurements were recorded as snapshots.

6. **Fig. Contact angle at pH 4.5 in SVF containing (a) Blank nanofiber (b) TT oil-loaded nanofiber, and (c) LCZ-loaded nanofiber**

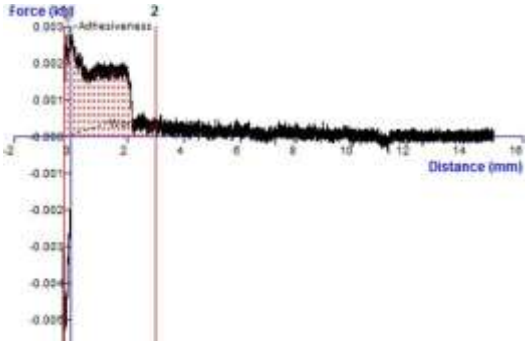
9. Mucoadhesive test:

The mucoadhesive strength of nanofiber was determined by using TA.XT plus texture analyzer, Stable Micro Systems, UK. A piece of 1.5 cm of nanofiber sample was attached to one side probe of the instrument and the vaginal mucosa of the goat was attached to the other probe. Both of these attachments were kept in contact for 15 seconds by applying a force of 5 gm. Then the required force of detachment for fiber from mucosa was calculated.

7. **Fig. Mucoadhesiveness of (a) blank nanofiber (b) TT oil-loaded nanofiber, and (c) drug-loaded nanofiber**



(a) (b)

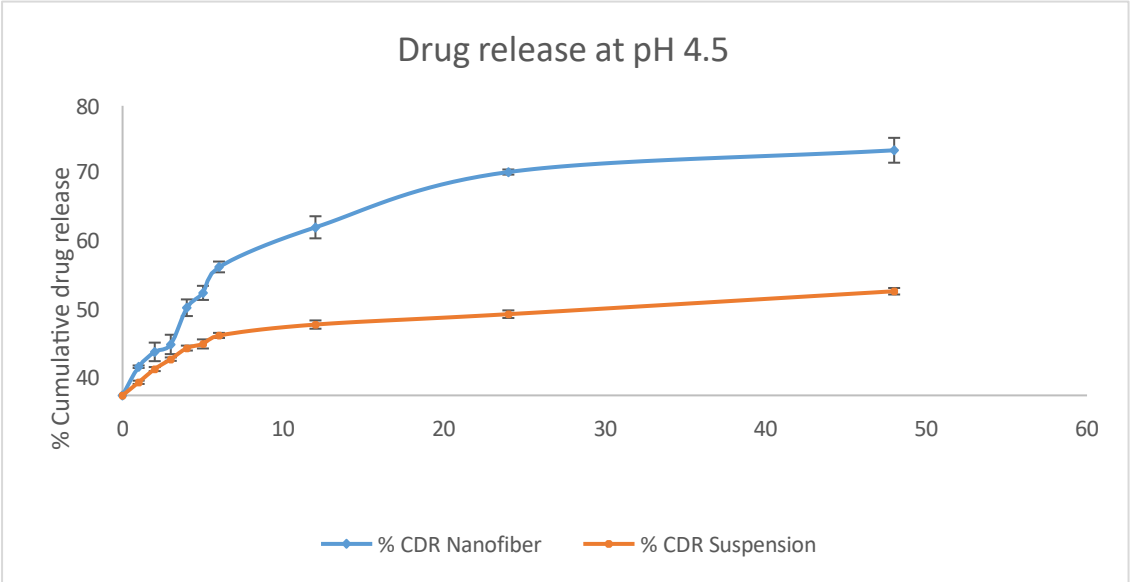


(c)

10. In vitro drug release study:

For the determination of drug release of the nanofiber, a piece of nanofiber mat (1×1 cm2) was weighed and kept in dialysis bag and then dipped in 100 ml SVF (pH 4.5) media in a shaker incubator. A temperature of 37 ± 0.5 ^{0}C with 75 rpm was maintained for the study. 5 ml of aliquots were withdrawn at different time intervals and 5 ml of fresh media were added after every withdrawal to maintain the sink condition. The concentration of the drug present in the aliquots was determined by using a UV-spectrophotometer at λmax of 299 nm. The percentage cumulative drug release of the optimized drug-loaded nanofiber sample was calculated.

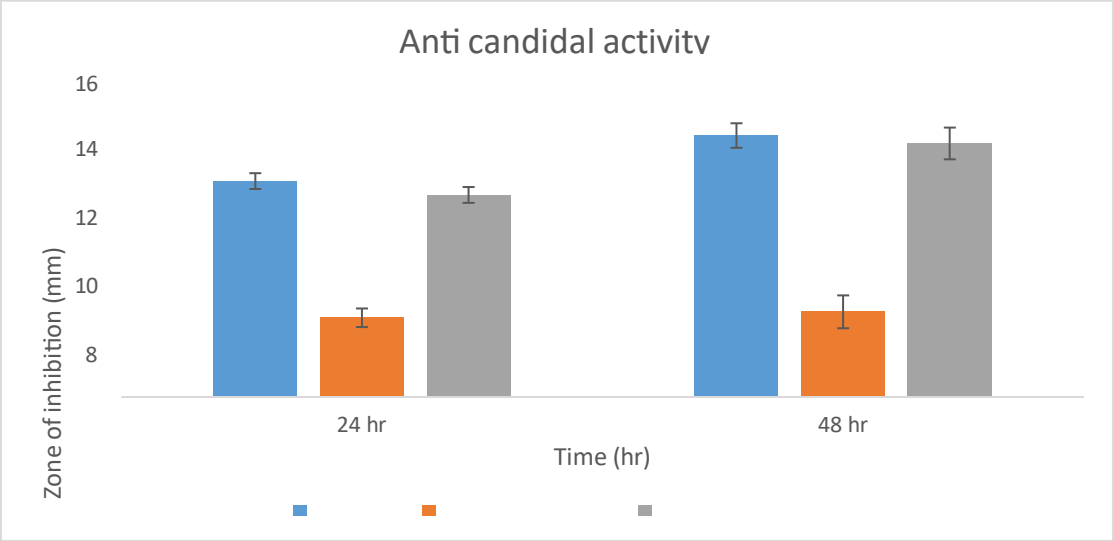
8. **Fig. In vitro drug release profile of drug-loaded nanofiber and drug suspension**



11. Anticandidal activity:

The anticandidal activity exhibited by nanofiber and LCZ disk is shown in Figure. The zone of inhibition (ZOI) of luliconazole-loaded nanofiber was 12.8 ± 0.53 mm after 48 hours which revealed the potential to inhibit C.albicans. TTO-loaded nanofiber possessed a small ZOI of 4.3 ± 0.30 mm indicating its anticandidal activity. The LCZ disk showed the ZOI of 13.2 ± 0.62. The ZOI of nanofiber was found nearer to the ZOI of LCZ disk which means that drug-loaded nanofiber also possesses anti candida activity which could help in the eradication of C.albicans at vagina. This demonstrates that TT oil added with LCZ in the nanofiber as an excipient may also provide an enhanced effect on its anticandidal capability. The blank fiber showed no ZOI against the candida albicans. From the results, it can be explained that electrospinning does not affect the anticandidal activity of luliconazole and LCZ-loaded nanofiber can be used as a better tool for the eradication of C.albicans infection.

9. **Fig. Anticandidal activity possessed by different nanofiber mats and LCZ dis**



12. Vaginal irritation study:

Vaginal irritation test was performed on female wistar rats (160-200 gm) which was approved by Institutional ethical committee, Jamia Hamdard, India (Protocol number - 1753) The rats were divided into three groups. First group of female wistar rat was exposed to polymeric nanofiber without drug (placebo) for 24 hours, second group was exposed to drug-loaded nanofiber and the third group was considered as control group (without any nanofiber). After 24 hours, visual examination of vagina was done and any type of irritation such as oedema and erythema was measured on a Draize scale by scoring it 0-4.

10. **Table. Samples scored on scale basis of erythema and oedema**

Samples applied	**Erythema**	**Oedema**
Control (Without any formulation)	0	0
Placebo nanofiber	0	0
Drug-loaded nanofiber	1	0

13. Storage stability study of nanofibers:

Stability study of drug-loaded nanofibers was checked at different conditions (4°C, 25°C±2°C/60%±5% RH and 40°C±2°C/75%±5% RH) using a stability chamber. Drug content, % drug remaining, and log% drug remaining were determined (Kamble RN et al.,2019).

11. **Table. Stability studies of drug loaded nanofiber at 4°C, 25°C±2°C/60%±5% RH and 40°C±2°C/75%±5% RH at predetermined time (n=3).**

Conditions (°C/RH)	**Time (Months)**	**Drug Conc mg/ml**	**% drug remaining**	**Log % drug remaining**
4°C	0	0.0504	98.05447471	1.99
	1	0.049	96.07843137	1.98

	3	0.048	94.11764706	1.97
	6	0.047	92.15686275	1.96
25°C±2°C/60%±5%	0	0.0499	97.84313725	1.99
	1	0.047	92.15686275	1.98
	3	0.0458	89.80392157	1.96
	6	0.0441	86.47058824	1.92
40°C±2°C/75%±5%	0	0.050	98.03921569	1.99
	1	0.048	94.11764706	1.97
	3	0.044	86.2745098	1.94
	6	0.042	82.35294118	1.91

SUMMARY AND CONCLUSION:

- The Ex-vivo permeation study showed that the permeation of the luliconazole drug with Tea tree oil was augmented with PCL/gelatin nanofibers from vaginal mucosa as compared to suspension and only Luliconazole loaded nanofiber.
- The adequate penetration may be due to the diameter of fiber in the nano range and also the use of tea tree oil helped as a penetration enhancer.
- From zone of inhibition obtained, drug-loaded nanofibers showed a powerful anticandidal activity.
- Therefore, can be used as a better tool for the eradication of C.albicans infection. Histological analysis after application of nanofibers confirmed no irritation signs on vagina. S
- Stability study of nanofiber at different conditions was found to be stable and can also be easily stored also at refrigerated condition. Therefore, this research detailed luliconazole nanofiber fabricated for the first time which successfully could work in the anticandidal action for the management of vaginal candidiasis.

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