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A NOVEL VAGINAL TABLETS LOADED WITH FLUCONAZOLE NANOSPONGES FOR VULVOVAGINAL CANDIDIASIS TO OVERCOME ANTIFUNGAL DRUG RESISTANCE

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ABSTRACT

The emergence of antifungal drug resistance needs a permanent solution for the treatment of Vulvovaginal candidiasis (VVC) among women. Fluconazole vaginal tablets using nanosponges as carrier was developed to fight the emerging fungal infections and to preclude increase of drug resistance strain. Nanosponges prepared using polymers like Ethyl Cellulose (EC) and Polymethyl methacrylate (PMMA), Polyvinyl alcohol (PVA) as a surfactant using emulsion solvent evaporation technique. The formulations were evaluated for interaction studies using DSC, SEM, XRD, FT-IR and *in-vitro* dissolution studies. Based on the above studies and results, the optimum formulations of nanosponges along with the tablet excipients was compressed into tablets. The tablets were evaluated for pre-compression and post compression parameters along with *in-vitro* release studies at pH 4.5 to mimic the vaginal medium conditions. Based on *in- vitro* dissolution studies of optimized formulation a good sustained effect with high drug concentration shows the applicability of fluconazole for local controlled delivery for the treatment of Vulvovaginal candidiasis.

KEYWORDS: Fluconazole, Vulvovaginal candidiasis (VVC), Antifungal drug resistance, Nanosponges, Mucoadhesive vaginal tablets.

INTRODUCTION

By the second half of 20th century, fungal diseases became one of the major ailments in large group of patients with impaired immunity. Fungal infections are said to be silent killers and cause suffering to millions of Population. The public health challenges in fungal infections are due to resistance of treatment methods and drugs used. This antifungal resistance represents a major challenge to clinicians responsible for treating invasive fungal infections due to limited arsenal of systemically available antifungal agents. Nanotechnology has become an interesting strategy to improve efficacy of traditional antifungal drugs, which allows lower toxicity, better biodistribution and drug targeting with promising results.

Vulvovaginitis is one of the common recurrent infection in reproductive aged women at some point of their life time. The *Candida albicans* is the most responsible pathogen in 90% of the infected cases and most of the remaining cases are due to *Candida glabrata*. Various diversified factors are responsible for the pathogenesis of Vulvovaginal candidiasis (VVC). So, it is impossible to find a treatment regimen, which is acceptable for all patients. It is found that antifungal regimens are different in its clinical effectiveness to be most safe and effective to be used by the practitioners and physicians.[1]

The treatment options of Vulvovaginal candidiasis (VVC) are limited due to antifungal resistance. This raised an urge in developing newer methods of drug delivery. The availability of drug concentration for a prolonged time after single administration by using vaginal tablets will help to adhere the drug to the mucosal vaginal tissue and can swell rapidly in aqueous environmental conditions. Mucosal vaginal tablets using nanostructured carriers can maximize the accumulation of drug molecule within non-healthy cells or tissues and can also lead the deep contact of drug within the biological membrane.

Fluconazole is a well-tolerated subclass of synthetic triazole antifungal drug, administered orally. Fluconazole is one of the promising drugs for the treatment of cryptococcosis and candida infections. Based on the liver enzyme levels in various studies it was found that fluconazole has the highest risk in causing liver injury and is found to be consistent in various cases with elevated level of serum liver enzymes.[2] Apart from the fluctuations in the serum

liver enzyme levels, fluconazole also causes untoward gastrointestinal side effects during oral administration.

The topically applied conventional vaginal formulations is having less retainability in vaginal epithelium, may be subjected to leakage and messiness leads to elimination of usage of those dosage forms by the patients. This led to the development of vaginal tablet using nanosponges as a carrier to bring a world of challenge in the treatment pattern of Vulvovaginal candidiasis (VVC), and also the other infections caused by *Candida albicans.*[3]

Drug targeting to a particular site can be developed by nanosponges; having tiny mesh like porous structure with unique ability to enclose the active drug molecule for various routes of administration. Nanosponges are the revolution in the treatment pattern by circulating the drug in the body and reaches a specific site, bind on receptors. These can release the drug in a controlled and predictable manner and thereby reduces the side effects, improved stability and helps to enhance the formulation stability.

Due to the increase in the development of drug resistant fungal strains, the development of new and innovative ideas using Nano based drug delivery systems for cellular targeting is predominant to improve the antifungal therapy.

The aim of this work was to prepare nanosponges using the polymers and its various combinations like Ethyl Cellulose (EC) and Polymethyl methacrylate (PMMA), PVA as a surfactant using emulsion Emulsion solvent evaporation technique. Solvent evaporation technique was considered as the best technique for preparation of nanosponges using Analytical hierarchy process (AHP) multi criteria as a decision-making tool. [4] The prepared nanosponges was subjected for evaluation studies. Vaginal tablets were prepared using the nanosponges as carrier by using direct compression with tablet excipients along with mucoadhesive polymers to develop controlled release mucoadhesive tablets.

MATERIALS AND METHODS[5,6,7]

Materials

Fluconazole (99.79%) was donated by Megasys Biotek, Koratty. Ethyl cellulose, PMMA, PVA were purchased from Nice chemicals, Ernakulam. Carbopol 940,Microcrystalline Cellulose,Magnesium stearate was also purchased from Ozone international Mumbai.

Chemicals used in the study were of analytical grade and used without further purification. Nanosponges were prepared by Emulsion solvent evaporation method.

Preparation of fluconazole nanosponges[8,9,10]

Fluconazole nanosponges formulated by emulsion solvent evaporation method. Various formulations of nanosponges (F01-F12) with varying proportions of Ethyl Cellulose, PMMA and the combination of Ethyl Cellulose (EC) and Poly methyl methacrylate (PMMA)were taken. The disperse phase consist of fluconazole(100mg) and required quantity of EC/PMMA dissolved in 20ml chloroform which was added slowly to a specific quantity of Polyvinyl alcohol (PVA) in 150ml of aqueous continuous phase. Then the mixture was stirred at 1000-1500rpm for 2hrs on a mechanical stirrer (ROTEK-250W) until the organic solvent was removed by evaporation. The nanosponges formed were collected by filtration and dried in Hot Air Oven (ROTEK). The dried nanosponges were stored in desiccator to remove residual solvent. The prepared nanosponges were characterized by various analytical techniques.

Table 1: Formulation of Fluconazole Nanosponges Using Different Polymer Ratios.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	100	100	100	100	100	100	100	100	100	100	100	100
EC(mg)	200	400	600	800	-	-	-	-	-	-	-	-
PMMA (mg)	-	-	-	-	200	400	600	800	-	-	-	-
EC:PMMA (mg)	-	-	-	-	-	-	-	-	400:200	400:300	400:400	400:500
PVA	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Chloroform (ml)	20	20	20	20	20	20	20	20	20	20	20	20

Formulation of mucoadhesive vaginal tablet[11,12]

Vaginal mucoadhesive tablets loaded with fluconazole nanosponges (F03, F07, F11) equivalent to 100 mg fluconazole were prepared using direct compression with Carbopol 940, microcrystalline cellulose and magnesium stearate. The ingredients (except: magnesium stearate) were passed through sieve No. 60 and mixed homogeneously for 15 minutes for direct compression. This blend was compressed using 8 mm size flat faced punch on (Cadmach) single punch compression machine. Tablet hardness was kept within the range of 7-10 kg.

Table 2: Formulation of Fluconazole Vaginal Tablet Using optimized nanosponges.

Ingredient	Quantity (mg)
Fluconazole loaded nanosponges	equivalent to 100mg fluconazole
Carbopol 940	60 mg
Microcrystalline Cellulose	45mg
Magnesium stearate	4mg

EVALUATION OF FLUCONAZOLE NANOSPONGES

Preparation of calibration curve of Fluconazole[13]

In the simple UV method aliquots of stock solution of fluconazole 0.1-1.0ml were transferred into series of 10ml volumetric flask and volume was made upto the mark using pH 6.8 phosphate buffer solution to produce concentration range 10-100µg/ml. The absorbance of each solution was measured at 261nm against the reagent blank(prepared similarly without the drug) by using Schimadzu UV-Visible Spectrophotometer. Calibration curve was prepared by plotting concentration v/s absorbance.

Drug polymer interaction studies[14,15]

FT-IR, XRD and DSC spectroscopic studies were used to study the drug-polymer interactions. The spectra were recorded by using the instrument Perkin Elmer spectrum IR Version 10.6.0, DSC Q20 V24.10 Build 122, Bruker D8 Advance-Twin respectively. Spectras of nanosponges containing the polymers of EC and PMMA were taken.

Percentage yield of nanosponges

The dried nanosponge were weighed and percentage yield was calculated with respect to the weight of equal quantities of drug and polymers used for the formulation. The percentage yield was obtained as the percentage ratio between practical and theoretical yield. The percentage yield was replicated for three times for each of the formulations.

$$\text{Nanosponges recovery}(\%) = \frac{recovered\ weight\ of\ nanosponges}{weight\ of\ polyme\ used+drug} \times 100$$

Drug entrapment efficiency

100mg of the prepared nanosponges were powdered and suspended in water and sonicated for 20 minutes. The drug was completely extracted from nanosponges by shaking for further 20 minutes. The above mixture was filtered through a 0.45 µm membrane filter, the resultant concentration was determined by using UV visible spectrometer at 261 nm. The entrapment efficiency was calculated by using the formula.

$$\text{Entrapment efficiency} = \frac{Actual\ \ weight\ of\ drug\ in\ sample}{Microspheres\ sample\ weight} \times 100$$

Surface morphology

Surface morphology and internal structure of products was observed by a Scanning Electron Microsope. Nanosponges were fixed on an aluminium step using a double-sided tube, sputter coated with gold to make the surface conductive and examine under microscope. SEM photographs JSM 6400 Scanning Electron Microsope at the 120x magnification at room temperature.

MICROMERITIC PROPERTIES

Angle of repose

The angle of repose of nanosponges was calculated by static method using funnel. The funnel was kept on triangular stand, which was kept on a horizontal plane at a height of 2 cm. The sample powder was introduced into funnel, until the pile was formed, till the tip of the funnel. The diameter of the pile was noted. The following formula was used to calculate the angle of repose.(θ)

$$\theta = \tan\text{-}1\ (h/r)$$

h= height of the pile of nanosponges

r=radius of the pile of nanosponges

Bulk density and tapped density

The bulk density and tapped density were determined by using tap density test apparatus (Kehra Instruments Ltd., Delhi). The Carr's index and Hausner's ratio were also calculated.

Determination of compressibility index

Carr's index gives the compressibility of a powder, it is calculated based on the formula

Carr's Index = (tapped density - bulk density / tapped density) x 100.

Determination of Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability. The Hausner's ratio is calculated by the formula

$$H = \rho T / \rho B$$

Where, ρB is the freely settled bulk density of the powder and ρT is the tapped density of the powder.

In-vitro dissolution studies[16]

The nanosponges were evaluated for their integrity in the physiological environment of the vagina. The nanosponges were tested for drug release for up to 9 hours in pH 4.5 to mimic the vaginal medium conditions. The *in-vitro* release tests was carried out using USP Type-1 dissolution test apparatus. Nanosponges equivalent 100mg Fluconazole were placed in 900ml pH 4.5 to mimic the vaginal medium conditions (dissolution medium) and the nanosponges were stirred at 150 rpm at 37±0.5°. An aliquot of the dissolution medium was withdrawn at predetermined time intervals and equivalent amount of fresh medium was added to it. The samples were analysed spectrophotometrically at 261 nm to determine the amount of drug released from the nanosponges.

EVALUATION OF FLUCONAZOLE VAGINAL TABLETS

Determination of post compression parameters and evaluation of tablets: The characterization studies like physicochemical properties, interaction studies using FT-IR, DSC and XRD. The formulated tablets were also subjected to weight variation test, hardness and friability, drug content determination, in vitro disintegration time, in vitro dissolution rate dissolution parameters.

In-vitro dissolution studies of vaginal tablets

The vaginal tablets were evaluated for their integrity in the physiological environment of the vagina. The tablets were tested for drug release for 9 hours in pH 4.5 to mimic the vaginal medium conditions.

The *in-vitro* release tests were carried out using USP Type-1 dissolution test apparatus. Vaginal tablets equivalent to 100mg Fluconazole were placed in 900ml at pH 4.5 to mimic the vaginal medium conditions buffer (dissolution medium) and were stirred at 150 rpm at 37±0.5°. An aliquot of the dissolution medium was withdrawn at predetermined time intervals and equivalent amount of fresh medium was added to it. The samples were analysed spectrophotometrically at 261 nm to determine the amount of drug released from the nanosponges.

RESULTS AND DISCUSSION

Physicochemical properties

The results of solubility, pH, moisture content, melting point, partition coefficient and derived properties of powder is depicted in table 3

Table 3: Physicochemical characterization of Fluconazole nanosponge.

Parameters	Results
Description	Fluconazole occurs as white crystalline powder
Solubility	Partially soluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.
pH	5.8±0.29
Melting point	139 ° C
True density (g/cc) ± SD	1.23±0.57
Bulk density(g/cc) ± SD	0.362±0.037
Compressibility index (%) ± SD	13.92±0.40
Hausner's ratio ± SD	1.67±0.16
Angle of repose(^{0}) ± SD	25.33^0± 0.72
Partition coefficient	3.2 at pH 7.4
Moisture content (%)±SD	7.92± 0.50

Table 4: The particle size distribution of Fluconazole powder.

Size range in µm	Number of particles
0-30	25
30-60	115
60-90	220
90-120	130
>120	35

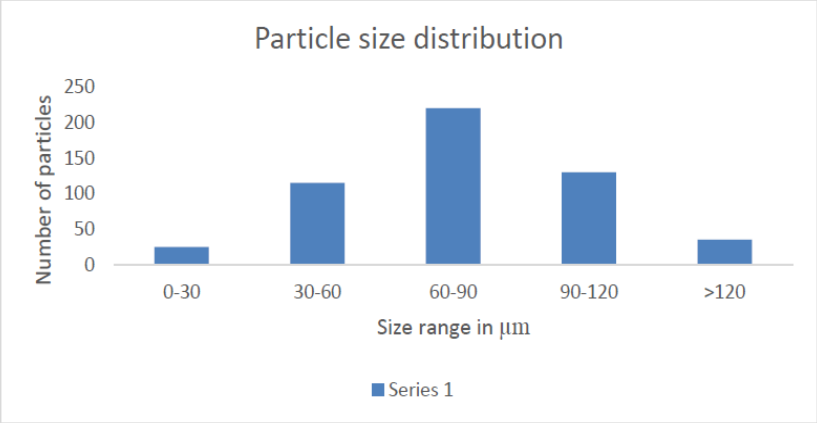

Fig.1: Particle size distribution of fluconazole powder.

The stock solution of Fluconazole at a concentration of 0.1mg/ml, shows maximum absorption at 261 nm. Fig 2 shows the calibration curve of Fluconazole, the correlation of the linear curve was found to be 0.996.

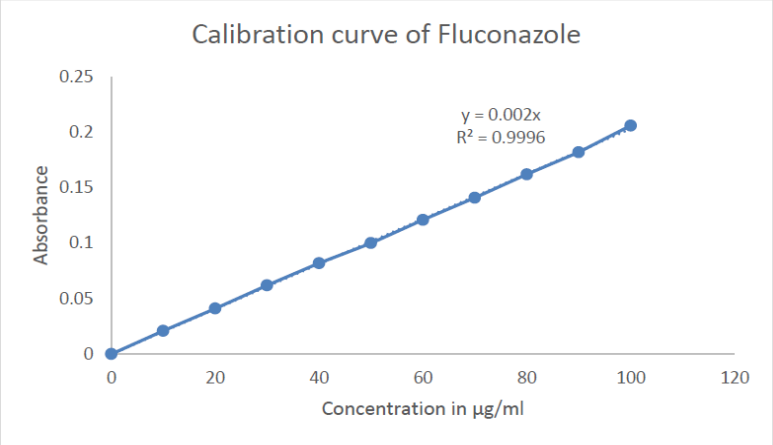

Fig. 2: Calibration curve of Flucoazole.

Differential Scanning Colorimetry

The physical and chemical changes within a sample are the function of temperature. The changes in the temperature due to loss or gain of heat can be measured by using differential scanning colorimetry (DSC). A sharp symmetric endotherm can indicate the relative purity of compound whereas the board asymmetric curve suggests the impurities or more than one thermal process. Endothermic peaks are obtained in the DSC spectra when the temperature falls below 120°C indicates the loss of water present in the compound. DSC analysis were performed to found out the physical nature of Fluconazole and to confirm the absence of drug polymer interaction in the formulation. Fluconazole shows sharp endothermic peak at temperature of 140. 41°C.From the Fig 3 & Fig.4 nanosponges it is confirmed that there is no interaction between the drug and polymers. The DSC curve of EC and PMMA nanosponges exhibit a less defined endothermic curve and a shift to lower temperature may be possibly due to the solubilization of drug in polymer or may be due to the high polymer ratio.

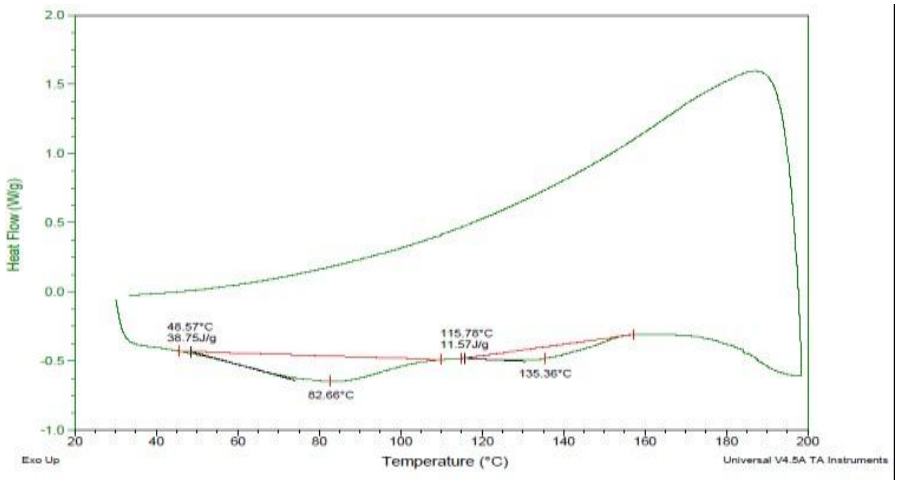

Fig.3: DSC of Fluconazole loaded EC nanosponges.

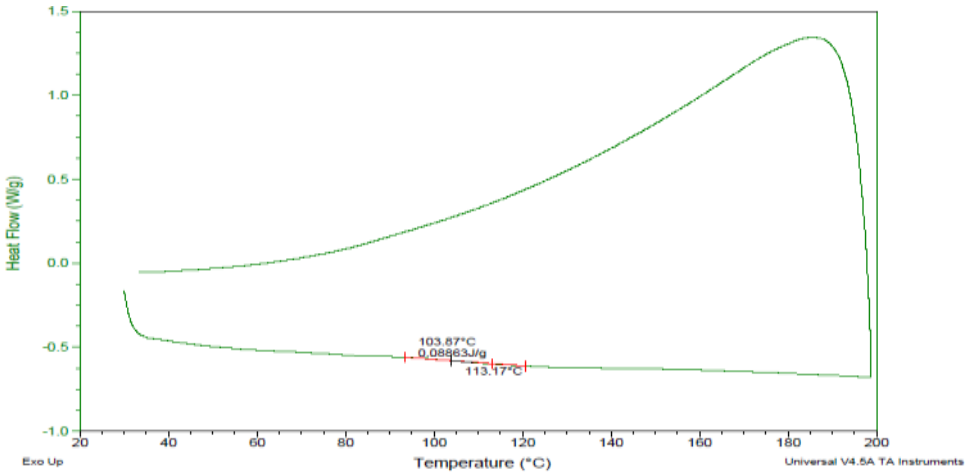

Fig.4: DSC of Fluconazole loaded PMMA nanosponges.

X-Ray Diffraction

Pure drug and Fluconazole loaded EC and PMMA nanosponges were analysed to find out whether the nanosponges of various drug polymer ratios are crystalline or amorphous. XRD of fluconazole revealed the presence of some peaks at value of 2θ lower than 30° having intensities, at 10°, 13.56°, 25.61°, 29.16°and some major signal at 20°, 16.70°, 16.51° of 2θ, the presence of numerous distinct peaks in the XRD spectrum of pure Fluconazole indicates that drug was crystalline in nature. On the other hand, the spectrum of EC nanosponges and PMMA nanosponges was characterized by Fluconazole peaks which are present in XRD patterns of nanosponges but with a reduction in number and intensity of peaks in of diffraction peaks, shows the characteristic of an amorphous compound. The enhancement in the targeted and sustained release by the nanosponges might have led to a decrease in the crystallinity of the drug in nanosponges. Fig 5 and Fig 6 depicts the XRD spectra of formulated nanosponges using EC and PMMA repectively.

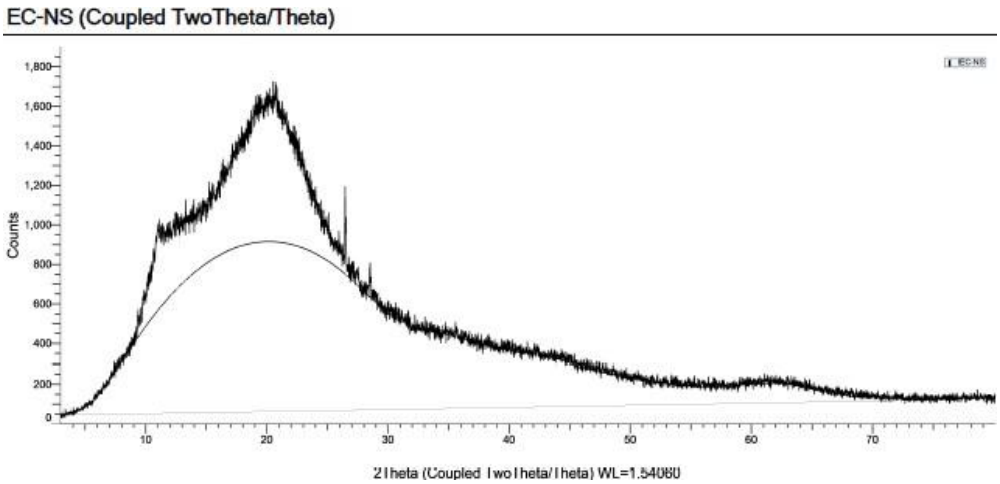

Fig.5: XRD of Fluconazole loaded EC nanosponges.

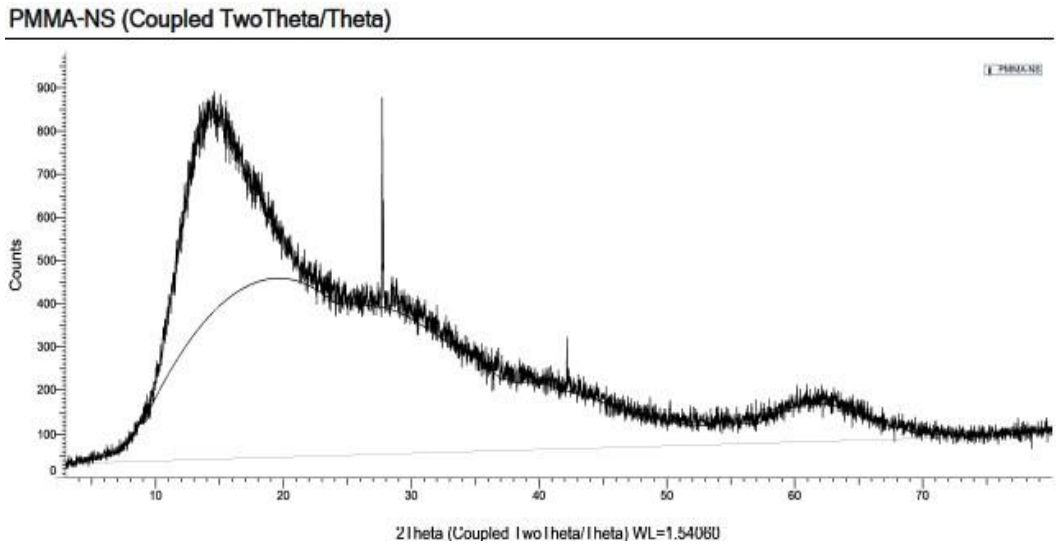

Fig. 6: XRD of Fluconazole loaded PMMA nanosponge.

Infrared spectroscopy

The infrared (IR) spectra of Fluconazole as well as its corresponding nanosponges shows that there are no interactions between their functional groups. The spectrum of fluconazole is complex due to presence of many groups such as triazolyl and 2, 4 difluroubenzyl. Sharp peaks at 965.82cm^{-1}and at 1135.93 cm^{-1} are due to triazolyl functional group. Various peaks representing different functional groups at 1082.04cm^{-1}, 1271.19cm^{-1}and at 1617.99cm^{-1}could be attributed to 2, 4 diflurobenzyl group. These peaks correspond to the stretching of O-H and CH group. The spectrum of EC was simple and had a sharp peak at 1051.77cm^{-1} which corresponds to CO-O-CO stretching. Fig 7 shows the peaks corresponding to IR spectra of fluconazole loaded EC nanosponges having peaks at 2973.72cm^{-1}. Widening of the symmetric and asymmetric valence vibrations of the ether bonds are present in the range of 1000-1200cm^{-1}. In fig 8 the presence of the polymer can be based on the following peaks, the most intensive peaks at 1700-1800cm^{-1} region in PMMA nanosponge.

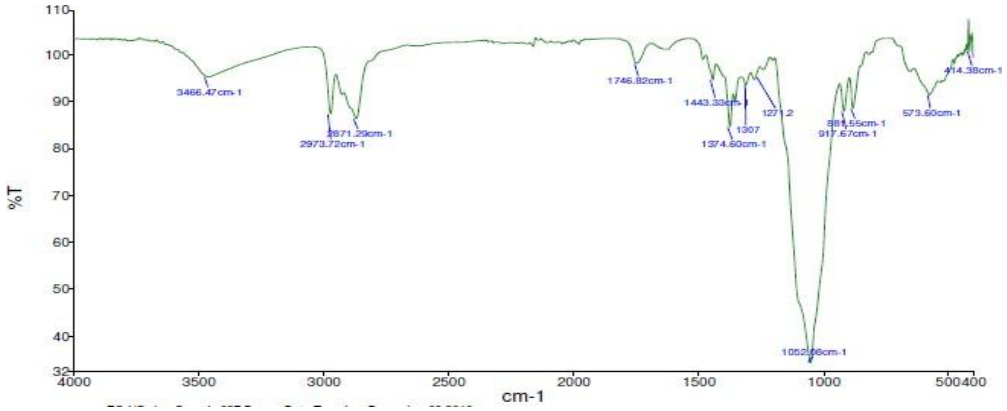

Fig.7: FT-IR of fluconazole loaded EC-Nanosponges.

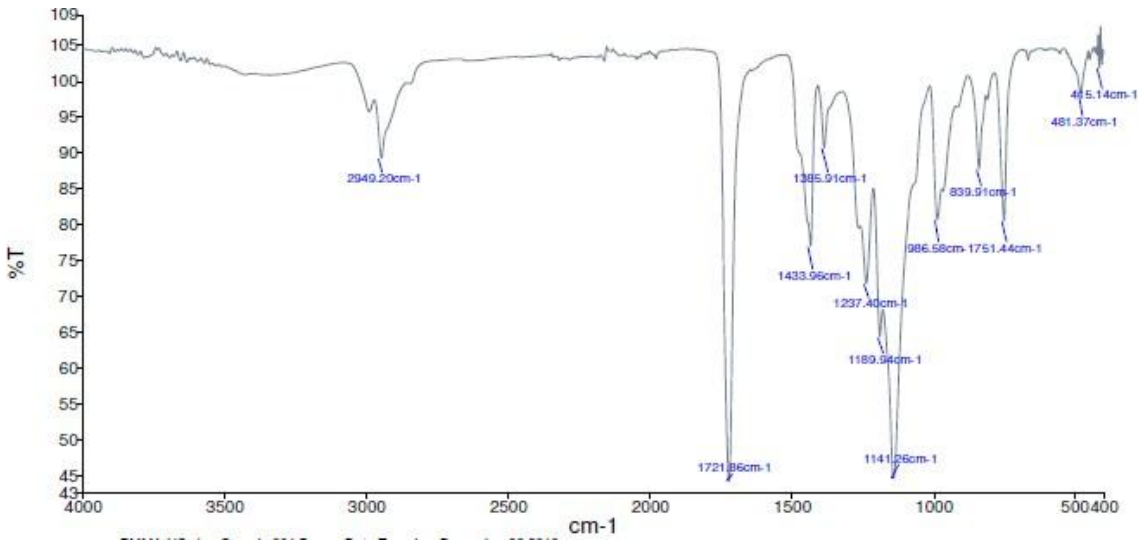

Fig. 8: FT-IR of fluconazole loaded PMMA-Nanosponge.

Percentage yield of nanosponges

The percentage yield of all the formulations of nanosponges were found to be 75% to 91.37%. The maximum percentage yield was found to be 91.37%, 90.62% and 91.22% in the formulation F03, F07 and F11 respectively. This confirms the uniform distribution of drug and polymers during processing which did not affect the yield of formulations.

Drug entrapment efficiency

All the formulations were analyzed for the drug entrapment efficiency. Triplicate readings were taken for the analysis of all formulation and average were taken for the optimization. The graphical representation of each formulated Fluconazole nanosponges entrapment efficiency was shown in Fig 9.

Table 5: Entrapment efficiency of Fluconazole nanosponges for controlled drug delivery.

Formulation code	Entrapment Efficiency	Formulation code	Entrapment Efficiency
F 01	80.5	**F 07**	90.6
F 02	83.5	**F 08**	86.23
F 03	89.5	**F 09**	85.44
F 04	83.56	**F 10**	79.55
F 05	84.4	**F 11**	87.22
F 06	80.12	**F 12**	81.3

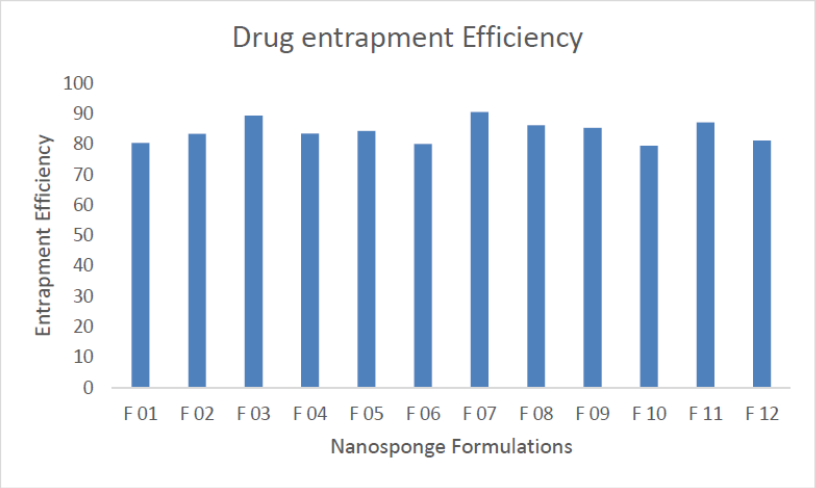

Fig. 9: Graphical representation of entrapment efficiency Formulation F01-F12.

Scanning electron microscopy

SEM results clearly showed the formation of nanosponges and were relatively spherical in shape and also showed there was only a small degree of agglomeration. Scanning Electron Micrographs of Fluconazole loaded EC nanosponges and Fluconazole loaded PMMA nanosponges are shown in Fig 10. Both the nanosponges were found to be porous in nature. Drug loaded nanosponges were having a smooth surface and with pores. These pores can act as points of entry for dissolution fluids. PMMA nanosponges were found to be more spherical and smaller in size. EC nanosponges were found to be more porous. Crystals of fluconazole visible at the surface; this presence might be involved with the initial burst effect.

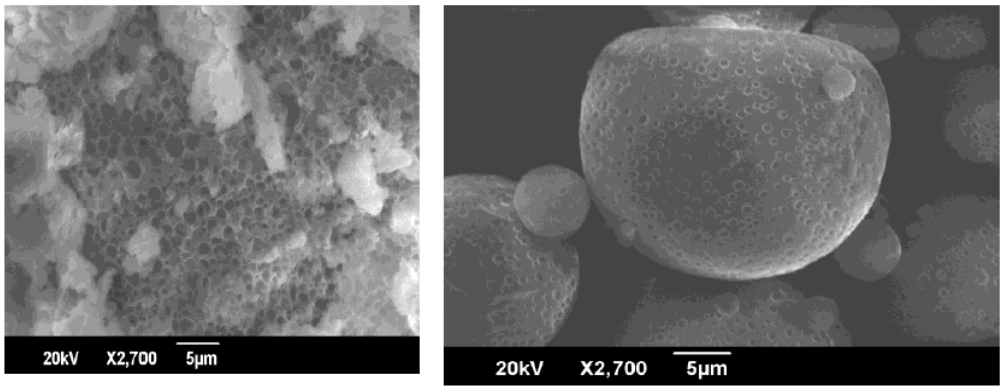

Fig.10: Scanning electron micrograph of fluconazole loaded EC nanosponges 5µm and fluconazole loaded PMMA nanosponges 5µm respectively.

Micromeritic properties

The prepared nanosponges were found to be porous and free flowing in nature. Angle of repose of all the formulations lies in the range of 23.11 to 26.060. Since the value is less than

25 - 30, all the formulation blend shows good flow property. The loose bulk density and tapped density for all the formulations varied from 0.580 - 0.596 g/cc and 0.633 - 0.650 g/cc respectively. The values obtained were found to be within the accepted range. There was no large difference seen between loose and tapped bulk density. These values were used in calculating % compressibility of the powder blend. Carr's index of the blends lie between 7.0202-8.373 which is ideal for good compressibility property. This shows that the formulations F01-F08 have good compressibility. Hausner's ratio for all the formulations lies in the range of1.071 -1.091. Since the value is less than 1.25, the blend has good flow. Table 6 shows the micromeritic properties of Fluconazole nanosponges.

Table 6: Micromeritic properties of fluconozole nanosponges.

Formulation Code	Angle of Repose	Loose Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio
F01	24.38	0.580	0.633	8.373	1.091
F02	25.66	0.590	0.640	7.813	1.085
F03	25.11	0.596	0.650	8.308	1.091
F04	23.11	0.585	0.638	8.307	1.091
F05	25.23	0.592	0.634	6.625	1.071
F06	25.16	0.596	0.641	7.00	1.076
F07	24.95	0.595	0.641	7.176	1.077
F08	24.76	0.581	0.633	8.215	1.090
F09	23.9	0.583	0.634	8.044	1.087
F10	25.11	0.596	0.645	7.597	1.082
F11	26.06	0.594	0.643	7.621	1.082
F12	24.76	0.589	0.634	7.098	1.076

***In-vitro* release studies**

The results obtained from in-vitro release studies were plotted in cumulative percent drug release Vs Time. The release data obtained for formulations F01 to F04 of nanosponges containing ethyl cellulose are obtained. The release rate of the formulations of F05 to F08 containing nanosponges of Polymethyl Methacrylate is tabulated. The release data obtained for formulations F09 to F12 are also tabulated of nanosponges loaded with both EC and PMMA. Fig 11 shows the release pattern obtained for formulations F01 to F04 of nanosponges containing ethyl cellulose.The release pattern of formulations F05 to F08 of nanosponges containing PMMA are shown in fig 12. Fig 13 show plots of release pattern of percent drug released as a function of time of the formulations containing of nanosponges loaded with both EC and PMMA.

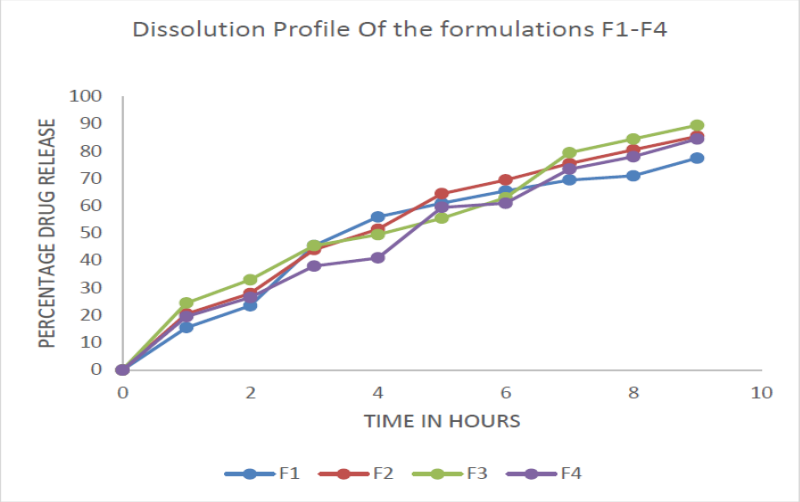

Fig. 11: *In vitro* release profile of Fluconazole nanosponges containing ethyl cellulose F01-F04.

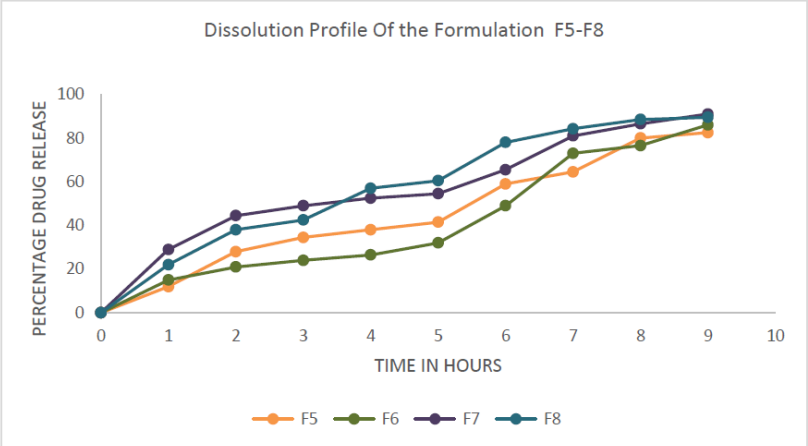

Fig. 12*: In vitro* release profile of Fluconazole nanosponges containing polymethyl methacrylate F05-F08.

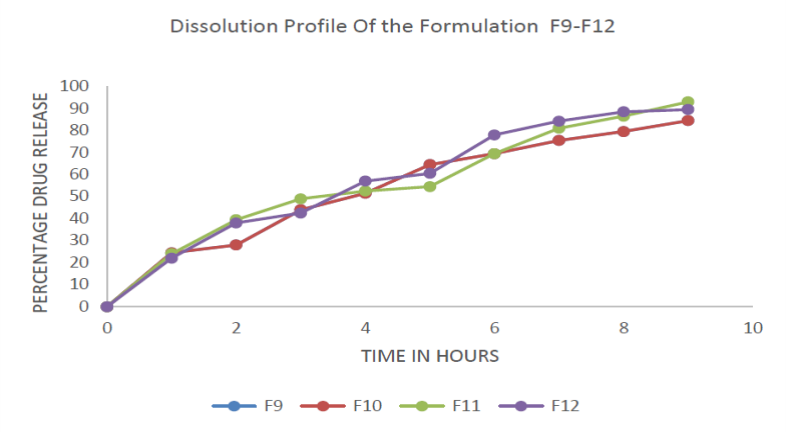

Fig.13: *In vitro* release profile of Fluconazole nanosponges containing ethyl cellulose and polymethyl methacrylate F09-F12.

The total amount of drug released for the formulations (F01 to F12) were 77.5%, to 93% observed at different time intervals for a period of 9 hours and the optimized formulations containing Ethyl cellulose nanosponge is F03,F07 and F11. This release rate was related to drug: polymer ratio. Increase of drug release was observed as a function of drug: polymer ratio. It was observed that the drug release decreased with an increase in the amount of polymer for each formulation. This may be due to the fact that the release of drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases. The release showed a bi-phasic pattern with an initial burst effect may be due to the un-entrapped drug adsorbed on the surface of the nanosponges. In the first hour drug release was found to be 15-30%. In general, all nanosponge formulations showed a prolonged release and no burst effect was observed. The overall trend shows decrease in release of FCZ from the prepared nanosponges with increasing polymer contents. Theoretically, this slower drug release is ascribed to increased path length for drug diffusion.

Post compression parameters and evaluation of tablets

The post compression parameters were performed in the compressed tablets and evaluated for the parameters like tablet hardness, friability, and weight variation drug content and disintegration time. Table 7 shows the results of tablet hardness, friability, and weight variation drug content and disintegration time.

Table 7: Evaluation of weight variation, hardness, friability, drug content uniformity and disintegration time.

Sl. No.	Parameters	Observed values
1	Weight Variation	Percentage deviation less than
2	Hardness (kg/cm^2)	5% 4.5 kg/cm^2 $\pm$ 0.002
3	Friability (%)	0.63 $\pm$ 0.001
4	Drug content uniformity %	94.37$\pm$0.002
5	Disintegration time (Min)	1.5 min$\pm$ 0.003

***In-vitro* Dissolution studies of the vaginal tablets containing optimized formulation of fluconazole loaded nanosponges.**

The tablets were subjected to dissolution studies in simulated vaginal fluid. The release profiles of vaginal tablets of Fluconazole containing optimized nanosponges were studied. As the presence of only EC in the matrix would not give the desired release profile of low initial drug release followed by improved release rate. From the dissolution data, of cumulative

percent of drug release against time, the optimized solid dispersion of delayed release tablets, the drug release can be extended up to 9 hours. The tablets is having a controlled release and exhibited a polymer concentration dependent release retardation effect. The cumulative percent of drug release was depicted in **Fig 14.**

Table 8: Percentage drug release of controlled release fluconazole formulations of vaginal tablets.

Time In Hours	VT1	VT2	VT3
0	0	0	0
1	19.5	24.5	24
2	30	39	39.5
3	45.5	44	49
4	44.5	52.5	52.5
5	51	59.5	60.5
6	63	69.5	70
7	75.5	81	84
8	79.5	86.5	89.5
9	85	89.5	90

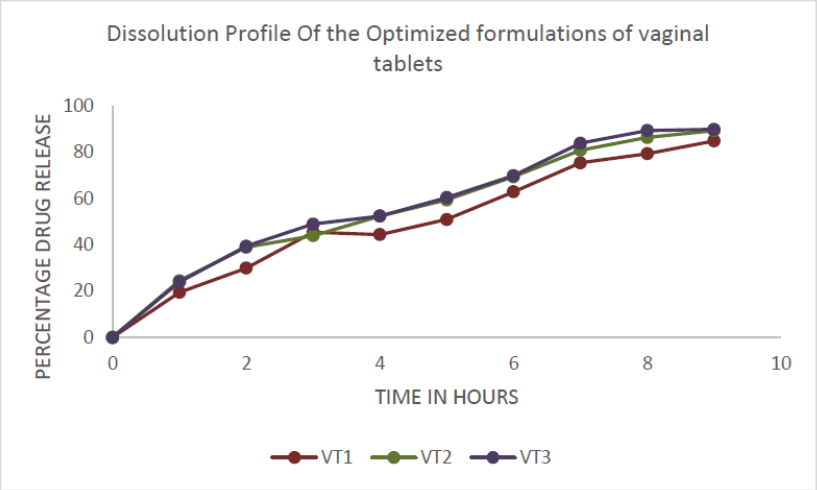

Fig. 14: In *vitro* release profile of Fluconazole formulations of vaginal tablets.

CONCLUSION

The present study was established with the development and evaluation of Fluconazole loaded nanosponges for the formulation of mucoadhesive vaginal tablets to treat Vulvovaginal candidiasis(VVC). Nanosponges were prepared with the blend of polymers, having good erodible properties in entrapment of drug and drug release. The application of AHP technique helped to select the best method for preparation of nanosponges from various alternatives. DSC and XRD were adopted in this investigation to identify the physical state of

the drug in nanosponges and it proved that the crystalline fluconazole transformed into the amorphous state after preparation. Nanosponges can be considered as a promising approach to solve the combating antifungal drug resistance. From the total results attained within the study indicates that mucoadhesive vaginal tablets has attractive properties and makes it convenient for successful treatment of Vulvovaginal candidiasis(VVC).

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