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Formulation and characterization of β-cyclodextrin Nanosponge of luliconazole for topical delivery

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ABSTRACT

Objective: Luliconazole is a BCS class-II topical broad spectrum imidazole antifungal agent which is used for the treatment of superficial dermatomycosis. It has poor aqueous solubility and less dermal availability. To overcome these problems the luliconazole is loaded into β-cyclodextrin nanosponges and incorporated into hydrogel for topical delivery.
Methods: The nanosponges are formulated using β-cyclodextrin (polymer) and Di-phenyl carbonate (cross linker) in different molar ratios (1:2, 1:4 and 1:6) by melting method. The drug is loaded by freeze-drying method with and without the addition of PVP K30. The physical parameters, drug content, *in-vitro* release studies are performed. The selected best formulation was loaded into carbopol-934 hydrogel. The physical parameters and *in-vitro* antifungal activity were performed.
Results: The results of the characterization of the best formulation were obtained 510.5 nm and -14.1 particle size and zeta potential respectively. The solubility also (0.0476 mg/ml) 14 folds increased when compared pure drug. The formulation loaded hydrogel exhibited good physical properties and *in-vitro* drug release after 12hours was found to be 84.78%. The *in-vitro* antifungal activity also (14.8mm) increased when compared to marketed cream (9.1mm).
Conclusion: This study revealed that prepared luliconazole loaded hydrogel has a great potential to improve the topical delivery of drug as compared with conventional cream.

Keywords: Luliconazole, nanosponges, hydrogel, β-cyclodextrin, dermatomycosis, solubility enhancement, PVP K30.

INTRODUCTION

Nanosponges are tiny mesh-like structures encapsulated with an outsized form of substances. They are spherical colloids nature with high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior[1].It is virtually accurate because the shape isn't really sponge-like a network of molecules in three dimensions together with long length polyester backbone. The typical diameter of nanosponge is below 1µm, but fractions below 500 nm are selected[2].Cyclodextrin (CD) is a biodegradable entity; it breaks down it gradually in the body. After reaching the targeted site, other systems generally unload most of the drug in a rapid and uncontrollable manner. Unlike other systems, nanosponges offer controlled release of medication which is one in all the most feature of such systems compared to other nanoparticulate delivery systems. β-CD has the best complexing ability and stability with cross-linking agents[3].In cyclodextrin based nanosponges (CD-NS), several cyclodextrins are come together by cross-linking with the linkers. Their inner central cavity serves as a pore of a regular sponge which capacity to incorporate substance in it. Hence, named as cyclodextrin nanosponge[4].It exhibits very high efficiency to accommodate poorly soluble molecules via inclusion and non-inclusion complexation. The presence of the lipophilic cavities of cyclodextrin monomers and hydrophilic channels the porous structure of CD-NS provides ability to incorporate a wide variety of

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compounds[4].Luliconazole is a topical broad spectrum imidazole antifungal drug[5]. It is originally developed in Japan for treating the superficial dermatomycosis and received marketing approval by Japanese health authorities in 2005 as a 1% cream, 1% solution and 1% ointment for the treatment of superficial mycosis including dermatophytosis, candidiasis and pityriasisversicolor. Then it is approved by USFDA on November, 2013 as 1% cream for the treatment of various forms of tinea infections (interdigitaletineapedis, tineacruris and tineacorporis) [6]. Chemically it is referred to as 2-[(2E, 4R)-4-(2, 4-dichlorophenyl)-1, 3-dithiolan-2-ylidene]-2-(1H-imdazole-1-yl) acetonitrile. It is found to inhibit the enzyme lanosteroldemethylase required for the ergosterol synthesis, which is major component in fungal cell wall[7]. It is active against dermatophytes like *C. albicans, Aspergillus fumigates* and *Trichophyton*species[8].

It has poor aqueous solubility and less dermal availability. Due to this reason, this study is aimed at developing a luliconazole loaded β-cyclodextrin nanosponge for topical delivery thereby, enhancing the aqueous solubility and to provide better dermal availability.

MATERIALS AND METHODS

Materials

Luliconazole was purchased from PureChem, Gujarat, India. β-cyclodextrin and diphenyl carbonate were procured from central drug house, New Delhi, India. carbopol – 934 P was gifted by Lubrizol and PVP K30 was purchased from jones chemicals, Madurai, India.

Methods

Determination of λmax

The absorption maximum of drug was determined by running the spectrum of drug in UV Spectrometer. 100mg of luliconazole was weighed accurately and dissolved in methanol and the volume was made up to (1000 µg/ml) 100ml using methanol. Further it was diluted to get (100 µg/ml) using the same diluent (sub stock solution). Finally this volume was made up to 100ml (10 µg/ml) using phosphate buffer pH 7.4. The spectrum of this stock solution was run in 200-400nm range in UV-spectrophotometer [5, 7].

Calibration of luliconazole in phosphate buffer pH 7.4

Calibration curve of the luliconazole was determined in phosphate buffer pH 7.4. From the sub stock solution having 100 µg/ml was serially diluted to concentrations of 2, 4, 6, 8, 10 And 12 µg/ml using buffer. These dilutions were analyzed at 299nm using UV-spectrophotometer[5, 7].

Preformulation studies

- Determination of solubility
- The solubility of pure luliconazole was performed in water, methanol, DMSO, acetone, acid buffer pH 1.2 and phosphate buffer pH 7.4.
- Drug-Excipient compatibility study

The drug-excipient compatibility studies of pure drug and physical mixture of drug with polymer were performed using FT-IR spectroscopy by the KBr disc method. The samples are mixed with potassium bromide in ratio of 1:100 and compressed to 10mm discs by hydraulic press at pressure of 150 bars for 30s.The samples were scanned between 4000 cm^{-1} and 400 cm^{-1}. The spectrum of pure luliconazole was compared with the spectrum of physical mixture.

Formulation of Luliconazole Nanosponges

Synthesis of β-cyclodextrin nanosponges

β-cyclodextrin nanosponges of different molar ratios are synthesized by melting method mentioned in Table1. The β-cyclodextrin (polymer) and diphenyl carbonate (cross linker) were grounded well in a mortar and melted in a flask at 90ºc for 5 hours. After the completion of reaction, it was allowed to cool and repeatedly washed with water. Then it was soxhleted with ethanol to remove the unreacted diphenyl carbonate and phenolic crystals. It was dried and stored for further use [9].

Preparation of luliconazole loaded nanosponges

Luliconazole was loaded in the synthesized β-CD nanosponges at the ratio of 1:4 (Drug : β-CDNS) with and without the presence of polyvinyl pyrrolidone (PVP K30) of total weight (Table-2).The drug was dispersed in aqueous colloidal dispersion of plain β-CDNS with 0.25% and 0.50% w/w of PVP K30. It was stirred continuously for 24 hours, and then centrifuged using a table top high speed refrigerated centrifuge at 2000rpm for 10 min to separate the uncomplexed drug as a residue below. Then the drug loaded nanosponges were obtained by freeze drying. The drug loaded nanosponge formulations were stored at room temperature for further use[10].

Characterization of LuliconazoleNanosponges

Production yield (%)

The production yields of the prepared nanosponges were calculated for each batch by dividing the practical mass of the nanosponge by the total amount of the drug and polymer[11].

$$\% \textbf{ yield} = \frac{\textbf{Practical mass of nanosponges X 100}}{\textbf{Theroetical mass (polymer + drug)}}$$

Determination of drug content

Luliconazole loaded nanosponges equivalent to 10mg of luliconazole was dissolved using methanol in the 100ml volumetric flask and the final volume was made up to 100ml using same. From the above solution 5ml was pipetted out and transferred to 50ml volumetric flask and the final volume was made with same methanol. Sample was filtered using 0.45µ syringe filter and the absorbance was measured at 299nm using UV spectrophotometer[8].

Determination of entrapment efficiency

An accurately weighed amount of luliconazole loaded

nanosponge equivalent to 10mg of luliconazole was taken in 20ml of methanol and centrifuged in to 10000 rpm at 4ºc for 30 minutes. Then the supernatant was removed and then estimate the free drug present in that at 299nm using UV spectrophotometer[8].

$$\% EE = \frac{Total\ amount\ of\ drug - Free\ drug \quad X\ 100}{Total\ amount\ of\ drug}$$

In-vitro drug release studies of luliconazole loaded nanosponge

In-vitro drug release of prepared luliconazole nanosponges was carried out by using dialysis bag method. In an open ended glass tube one end was tied with dialysis bag and the luliconazole loaded nanosponge equivalent to 1% of luliconazole was placed. Then dipped in to the 200ml of the pH 7.4 phosphate buffer, ran it with magnetic stirrer at 300rpm. Aliquots of 2ml of sample were withdrawn at frequent time intervals and transferred in to a 10ml volumetric flask and the volume was made up to 10ml using pH 7.4 phosphate buffer. The sink condition was maintained by replacing it with 2ml of fresh medium. The samples were filtered and measured at 299nm using UV-spectrophotometer[8].

Selection and Evaluation of Best Formulation

The selection of best formulation is based on the results obtained from drug content, entrapment efficiency; *in-vitro* drug release studies. The selected formulations were evaluated for FT-IR study, surface morphology, particle size & zeta potential and solubilization efficiency.

FT--IR Spectroscopical studies

Infrared spectrum (IR) analysis was carried out for the selected best formulation to find out the interactions between the drug and excipients used as per the procedure mentioned on drug polymer interaction studies.

Scanning Electron Microscopy (SEM)

Morphological evaluation of the selected Nanosponges formulation was carried out in scanning electron microscope (SEM) (Hitachi X650, Tokyo, Japan).All samples were examined on a brass stub using carbon double-sided tape. Powder samples are glued and mounted on metal sample plates. The samples are gold coated (thickness ≈15–20 nm) with a sputter coater (Fison Instruments, UK) using an electrical potential of 2.0 kV at 25 mA for 10 min. An excitation voltage of 20 kV was used in the experiments[12].

Particle size and zeta potential

The particle size distribution was determined by using dynamic light scattering (DLS) technique (Malvern particle size analyzer, Nano ZS 90, Malvern Instruments Ltd., UK). In this technique the particle sizes of nanosponges were observed. The polydispersity index (PDI) was calculated from the standard deviation and mean particle size of the nanosponges, The polydispersity index is the indication for the nature of dispersity. The freeze dried powders are redispersed with water to obtain a proper scattering intensity before measurement[11, 13].

Solubilization efficiency

The solubilization efficiency of optimized formulation was investigated for their solubilization enhancement capacity as compared to the pure drug. The weighed amount of 10mg of luliconazole and the prepared luliconazole loaded nanosponge equivalent to 10 mg of luliconazole were dispersed separately each in 10 ml of distilled water. They were placed on the mechanical shaker at ambient temperature. After equilibrium (24hr), the obtained suspension was centrifuged at 10000 rpm for 10min and, the supernatant was analyzed for luliconazole concentration at 299nm using UV-visible spectrophotometer. This was repeated by replacing the distilled water with phosphate buffer pH 7.4.

Drug release kinetics

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted to various mathematical models such as zero order, first order, Higuchi matrix, Hixon-crowell cube root law and Korsmeyer- Peppas equation. The regression co-efficient values were calculated. In this by comparing the regression coefficient values obtained, the best fit model was selected[14].

Formulation of Luliconazole loaded Nanosponge gel

Accurately weighed amount of carbopol 934 was taken and mixed in distilled water (preheated). Uniformity of stirring was maintained and then gel was kept in refrigerated condition for 24hrs. To the weighed amount of carbopol gel base, luliconazole nanosponges equivalent to 1 %w/w of luliconazole were uniformly dispersed. Propylene glycol was added as a penetration enhancer. Methylparaben and propylparaben were added as a preservative was showed in Table 3.Triethanolamine was added drop wise with gentle stirring using a homogenizer for adjusting the pH[15].

Evaluation of luliconazole loaded nanosponge gel[15]

- Physical appearance
- The prepared nanosponge gel was visually examined for consistency, color and homogenecity.
- Determination of pH
- Onegm of prepared luliconazole loaded nanosponge gel was dissolved in to the 100ml of distilled water and the pH was determined by using digital pH meter.

Determination of viscosity

Viscosity was determined by Brookfield's viscometer, using spindle no.s64 with an optimum speed of 100 rpm was used to measure the viscosity of the preparation.

Determination of spread ability

Accurately weighed 1gm of prepared luliconazole loaded nanosponge gel was placed on the pre-marked glass slide and that was sandwiched with another slide had same dimension. Then 500gm of weight was placed on the top of the upper slide for 5 minutes. The increase in the diameter due to spreading of gel was noted down.

Spread ability = M x L/T

Where, M = mass in grams, L = distance traveled by gel, T = time taken in seconds.

Determination of content uniformity

The drug content of the prepared luliconazole loaded nanosponge gel was carried out by dissolving accurately weighed quantity of equivalent to 20mg of the luliconazole in a beaker containing 10ml of methanol. Stir the solution for 30 minutes and centrifuged in high speed cooling centrifuge and 2ml of the solution was made up to 50ml with phosphate buffer pH 7.4. Then from the above solution 2.5ml of sample was made up to 10ml using the phosphate buffer pH 7.4. The samples were analyzed spectrophotometrically at 299nm against blank using UV-visible spectrophotometer.

In-vitro drug release studies

In-vitro drug diffusion study was performed using dialysis bag. The nanosponge gel equivalent to 20mg of luliconazole was placed in a dialysis bag; both sides were tied with thread. That acted as donor compartment. Then the bag was placed in a beaker containing 20ml phosphate buffer pH 7.4 which acted as receptor compartment. The temperature of the receptor medium was maintained at 37º±2ºc and the medium was stirred at a speed of 100rpm using a magnetic stirrer. 2.5ml of the samples were collected at a predetermined time and replenished immediately with the same fresh volume of buffer phosphate buffer pH 7.4. The sink condition was maintained throughout the experiment. The samples were analyzed at 299nm using UV- visible spectrophotometer[8].

In-vitro Antifungal activity

Candida albicans was used for determination of antifungal activity of optimized nanosponge loaded hydrogel. Antifungal activity was determined by sabourauds dextrose agar diffusion test using 'cup plate technique' on Petri plates of uniform size which were pre sterilized in an autoclave. In 20ml of molten sabourauds dextrose agar medium, 100µl of the fungal inoculum was seeded and then poured into the assay plates. Theses plates were allowed to cool down on leveled surface and were further died for 15 min at room temperature. Wells were cut out of solidified agar medium using sterilized iron bore each of 1cm in diameter, and 100 mg of the prepared gel was placed into each well. Marketed Luliconazole (1%) cream acting as positive controls were used to compare the inhibition zone of optimized.

RESULTS AND DISCUSSION

Determination of λmax

- The drug solution (10µg/ml) exhibited the absorption maximum (λ_{max}) at 299nm in phosphate buffer pH 7.4 in Fig.1.
- Calibration of Luliconazole in Phosphate buffer pH 7.4
- The absorbance of the drug solutions in the range of 2-12µg/ml were measured at 299nm. It showed the linearity of r^2=0.999 in the phosphate buffer pH 7.4 in Fig.2.

Preformulation studies

- Determination of solubility
- The pure luliconazole was freely soluble in DMSO, soluble in acetone and methanol and insoluble in water, acid buffer pH 1.2, phosphate buffer pH 7.4.
- Drug-Excipient compatibility (FT-IR) studies

FT-IR spectroscopy was used to investigate the interactions between and drug. The FT-IR spectral analysis of luliconazole alone showed that the principal peaks were observed at wave numbers confirming the drug. The major peaks of luliconazole were observed a wave numbers 3039, 2613, 2569, 2239, 1100 and 656 cm^{-1}. It was confirmed that there are no major shifting as well as any loss of functional peaks between the spectra of pure drug and the physical mixture. The drug and physical mixture was confirmed that are no interaction between the drug and polymers which was shown in Fig.3-9.

Characterization of Luliconazole Nanosponges

Production yield

The production yield of the prepared nanosponges was increased with increasing in the polymer ratio against cross-linker. Addition of PVP K30 (0.25%, 0.50% w/w) as channelizing agent will also increased the production yield were shown in Fig-11.

Determination of Drug content

The drug content of formulations (F1 to F9) ranges from 83.25% to 98.37%. among the formualtions F8 showed the maximum drug content (98.37%) so F8 was the best formulation among the nine formulations. The variation in the drug content between the formulations were shown in Fig.12 and Table-4.

Determination of Entrapment Efficiency

Percentage entrapment efficiency for the prepared nanosponges were observed in the range from 52.80% to 94.21% (Fig.13). Among the nine formulations with different polymer ratios, F8 showed the highest % entrapment efficiency of 94.21%. The reason for the high entrapment was due to the addition of 0.50% w/w of Polyvinylpyrrolidone K30, which made the ternary complex between the β-cyclodextrin nanosponges and Drug.

In-vitro Drug release studies of Luliconazole loaded Nanosponges

The cumulative percentage drug release of all the nine formulations were in the range of 62.94% to 86.76% (Fig.14 - 16).The increased drug release of formulations F4 to F9 were due to addition of 0.25% w/w and 0.50% w/w of PVP K30, which acted as channelizing agent and also increased the drug release from the nanosponges. Thus, it was expected that the increased concentration of cross linker, which retarded the release of luliconazole from nanosponge formulations might be useful for controlling its release. The F8 formulation showed the controlled release due to increase concentration of cross linker, but formulations F6 and F9 showed the intermediate release, this may be happened because of insufficiency of the nanocavities on the surface of nanosponges which depend on the concentration of cross linker.

Selection and Evaluation of Best Formulation

From the results obtained upon the characterization of all the nine formulations (F1 to F9), **F8** was found to be best formulation.

FT-IR spectroscopical studies

The peaks obtained in the pure luliconazole were also found in optimized formulation (F8), which indicates that there is no interaction between the drug and excipients. The peak observed at wave number 1781 cm^{-1} was indicated (Fig.17) the formation of carbonate bond in the β-cyclodextrin nanosponge, which ensures the complete formation of nanosponge.

Particle size and zeta potential

The SEM images (Fig.18) showed the crystalline nature of the optimized formulation F8. The average particle size of the luliconazole loaded nanosponge was 510.5nm with the Polydispersity index of 0.387 (Fig.19) and the zeta potential was found to be -14.1mV (Fig.20) which showed the moderate stability of the nanosponges.

Solubilization Efficiency

Luliconazole loaded nanosponge formulation (F8) showed the highest solubility in distilled water 0.0476 ± 0.0017 mg/ml as compared with pure drug 0.0034 ± 0.006 mg/10ml and also in phosphate buffer pH 7.4 the solubility of the pure drug and formulation F8 were found to be 0.0041 ± 0.0017 mg/ml and 0.0574 ± 0.0024 mg/ml. Thus the solubility of nanosponge formulation was increased in 14 times when compared to pure drug.

Drug release kinetics

The best selected *in-vitro* release data of optimized formulation (F8) were fitted to various mathematical models such as Zero order, Higuchi and Korsemeyer-peppas kinetic models. The highest regression (r^2=0.995) was obtained for zero order kinetics followed by Higuchi (r^2=0.946) and korsemeyer-peppas (0.997) model. The controlled release mechanism was studied by zero order and diffusion of drug by Higuchi model. The 'n' value of the korsemeyer-peppas model was found to be 0.899, it described that the drug was released by super case II transport i.e., the drug release was dependent on both drug diffusion and polymer erosion were shown in Fig.22-24.

Evaluation of Luliconazole loaded Nanosponge Gel

Physical appearance

Prepared nanosponge loaded gel was homogenous in nature, smooth in consistency as seen in Fig.25. There was no separation observed in the prepared gel.

Determination of pH

The pH of 1% aqueous solution of the prepared luliconazole nanosponge gel was found to be **6.89 ± 0.5**at 25ºc.

Determination of viscosity

The viscosity of the prepared nanosponge gel was found to be **$3.565x10^6$ cps**, which is considered enough viscous for topical application.

Determination of spreadability

Spread ability of the prepared nanosponge gel was found to be **9.3±0.284 gm.cm/sec**. it was considered as good for topical application.

Determination of content uniformity

The content uniformity of the prepared nanosponge gel was found to be **93.15±0.65 %.**

In-vitro drug release study

The cumulative percentage drug release after 12 hours for prepared nanosponge gel was found to be 84.78 ± 0.379 %.was shown in Table- 5 and Fig. 26.

In-vitro Antifungal activity

The *in*-vitro antifungal activity of the marketed 1% cream and the prepared luliconazole nanosponge gel were showed in the Fig.27. The zone of inhibition for marketed cream and luliconazole nanosponge gel were found to be 9.1 mm and 14.8 mm respectively was shown in Table-6.

Table1: Synthesis of β-CDNS

Formulation code	β-CD : DPC (in molar ratio)
NS1	1: 2Tabl
NS2	1: 4
NS3	1: 6

Table 2: Drug Loading in to Nanosponges

Formulation code	Drug: Nanosponge Ratio		% of PVP K30 (of total preparation weight)
	NS	Drug : NS	
F1	NS 1	1 :4	-
F2	NS 2	1 :4	-
F3	NS 3	1 :4	-
F4	NS 4	1 :4	0.25% w/w
F5	NS 5	1 :4	0.25% w/w
F6	NS 6	1 :4	0.25% w/w
F7	NS 7	1 :4	0.50% w/w
F8	NS 8	1 :4	0.50% w/w
F9	NS 9	1 :4	0.50% w/w

Table 3: Preparation of Luliconazole loaded Nanosponge Gel

S. NO	INGREDIENTS	QUANTITY
1	Luliconazole nanosponge	Equivalent to 1%
2	Carbopol 934 (1%w/v)	20g
3	Ethanol 95%	2 ml
4	Propylene glycol	0.9 ml
5	Triethanolamine	q.s
6	Propyl paraben	0.006 gm

Table 4: % of Drug content

S. No	Formulation code	% Drug content
1	F1	83.25 ± 1.24
2	F2	85.78 ± 0.99
3	F3	87.37 ± 1.40
4	F4	93.54 ± 0.65
5	F5	95.90 ± 0.34
6	F6	91.6 ± 1.50
7	F7	92.19 ± 0.83
8	F8	98.37 ± 0.83
9	F9	89.51 ± 0.81

Table 5: In-vitro drug release luliconazole nanosponge Gel

Time (hours)	Luliconazole nanosponge Gel	
	Mean	± SD
0	0	0
1	4.68	0.158
2	13.82	0.289
3	24.41	1.075
4	30.58	0.729
5	38.54	0.781
6	47.67	1.281
7	55.61	0.511
8	63.49	0.496
9	69.84	0.438
10	74.93	1.28
11	78.31	0.435
12	84.78	0.379

Table 6: Zone of Inhibition

S. No	Formulation	Antifungal activity (zone of inhibition) in mm
1	Marketed cream	9.1 mm
2	Luliconazole nanosponge Gel	14.8 mm

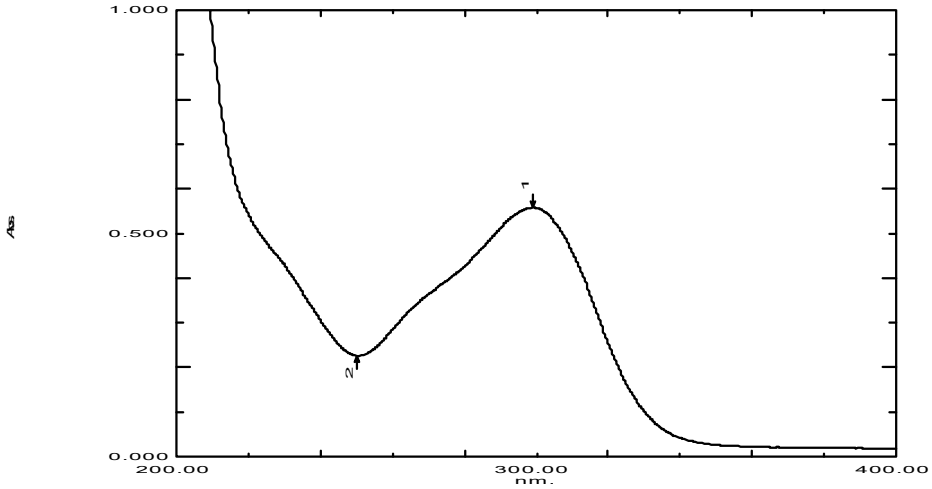


Fig1: λmax of Luliconazole

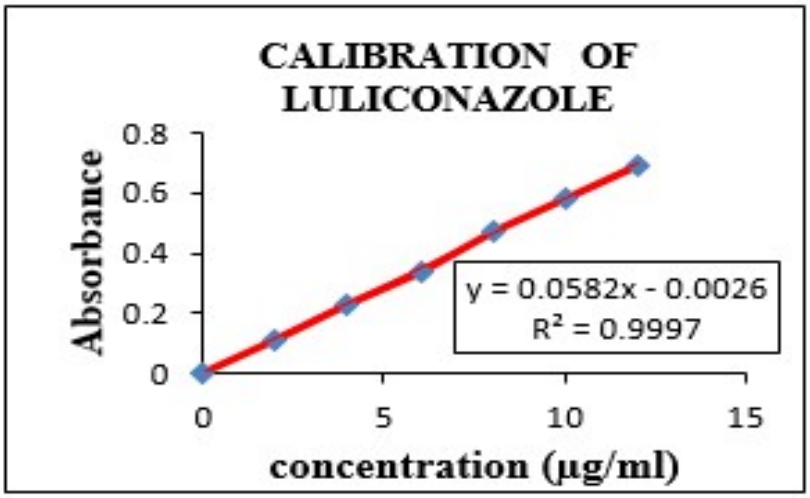


Fig 2: Calibration of Luliconazole

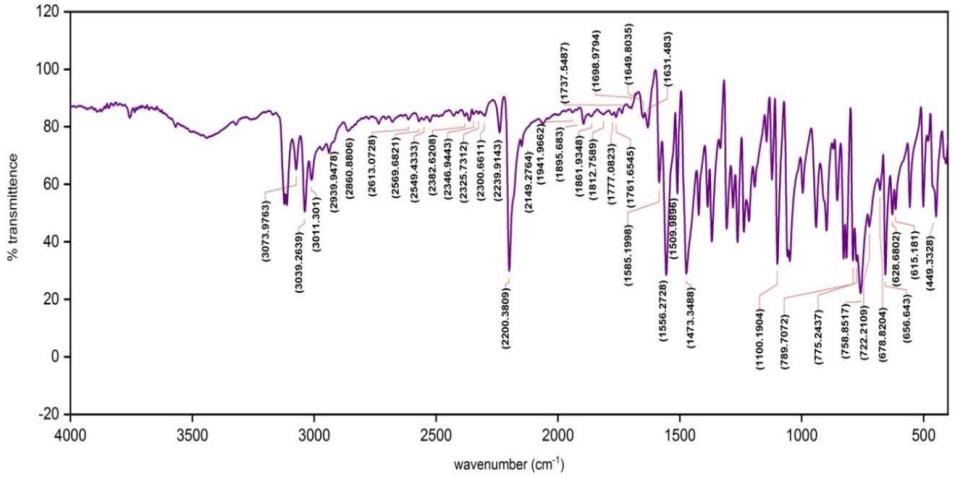


Fig 3: FT-IR of pure Luliconazole

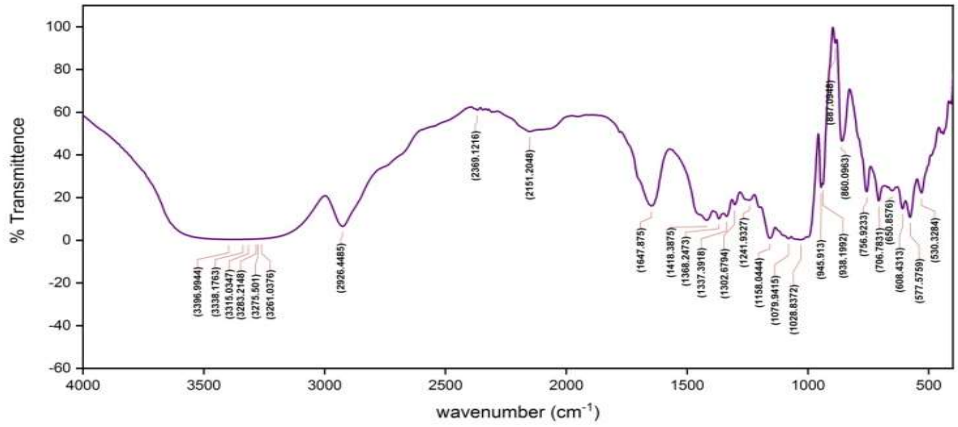


Fig 4: FT-IR of β-cyclodextrin (BCD)

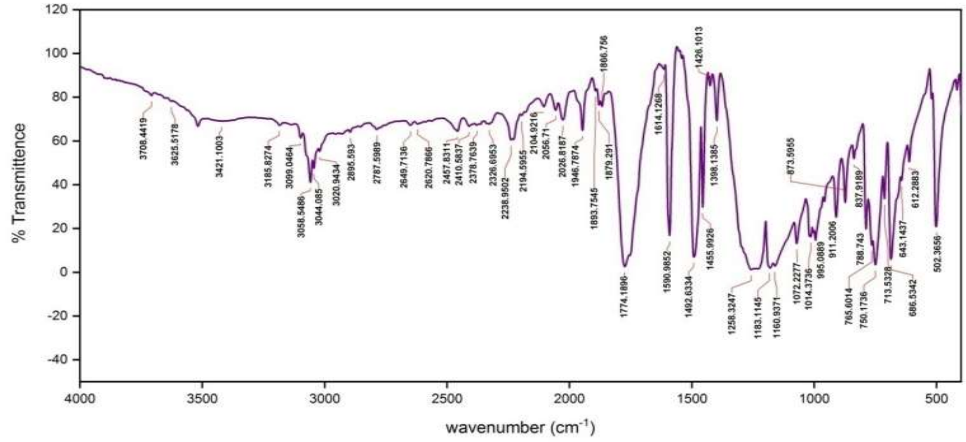


Fig 5: FT-IR of Diphenyl carbonate

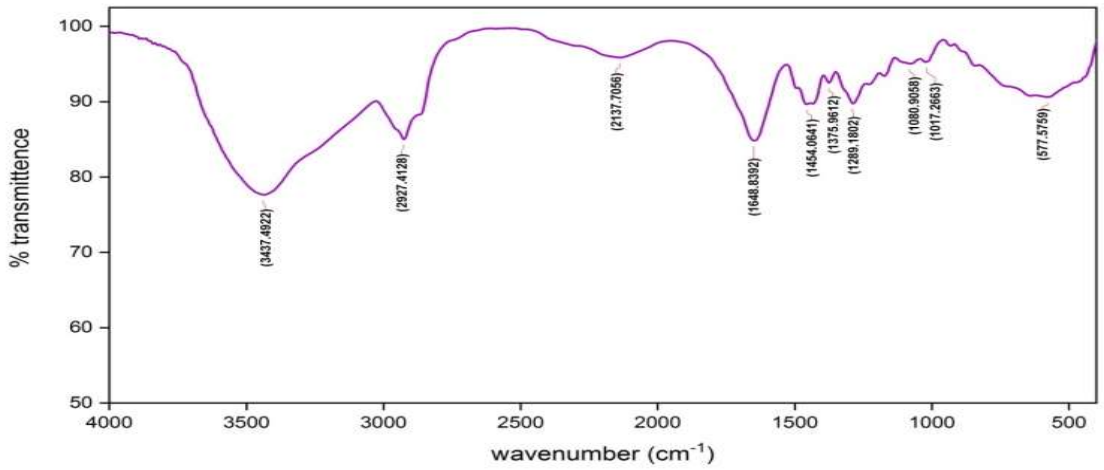


Fig 6: FT-IR of PVP K30

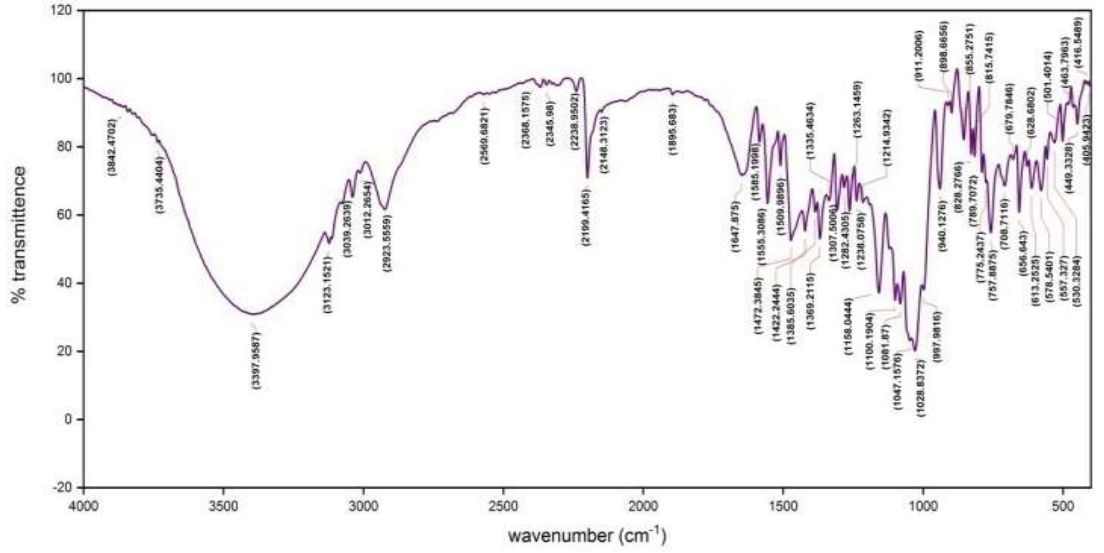


Fig 7: FT-IR of Drug + BCD

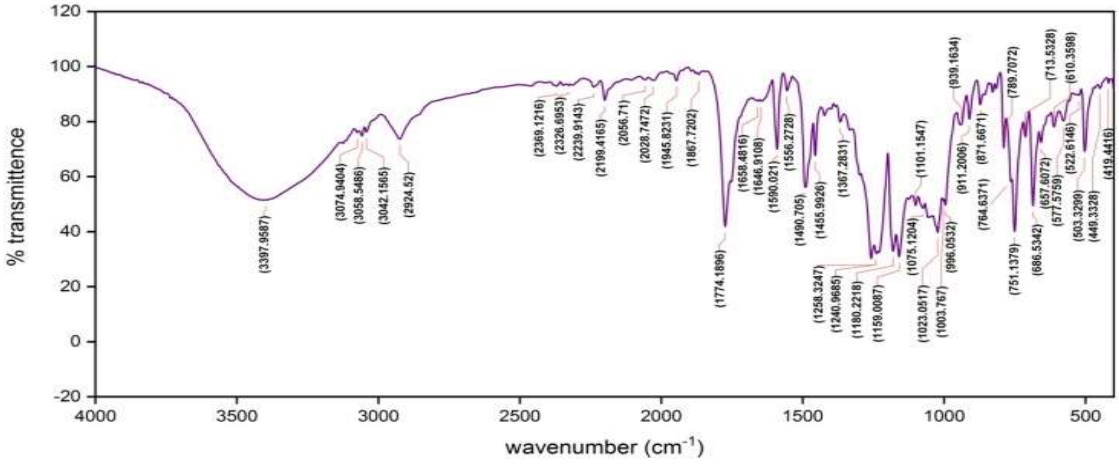


Fig 8: FT-IR of Drug + BCD + DPC

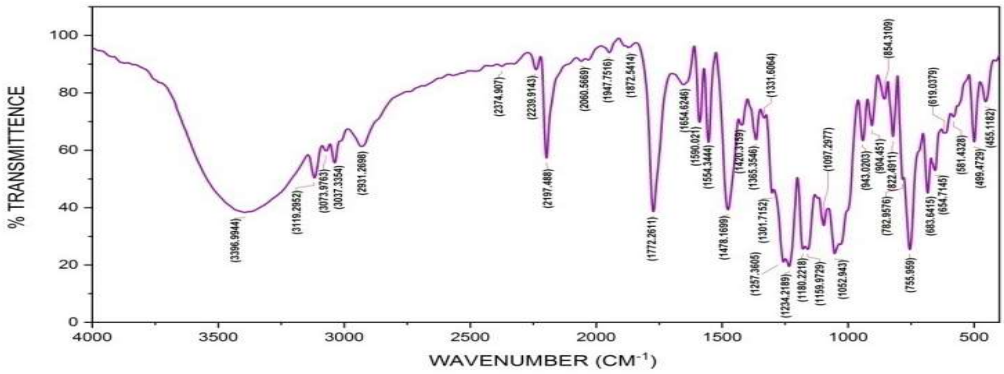


Fig 9: FT-IR of Drug + BCD + DPC + PVPK30

Fig 10: Luliconazole nanosponges

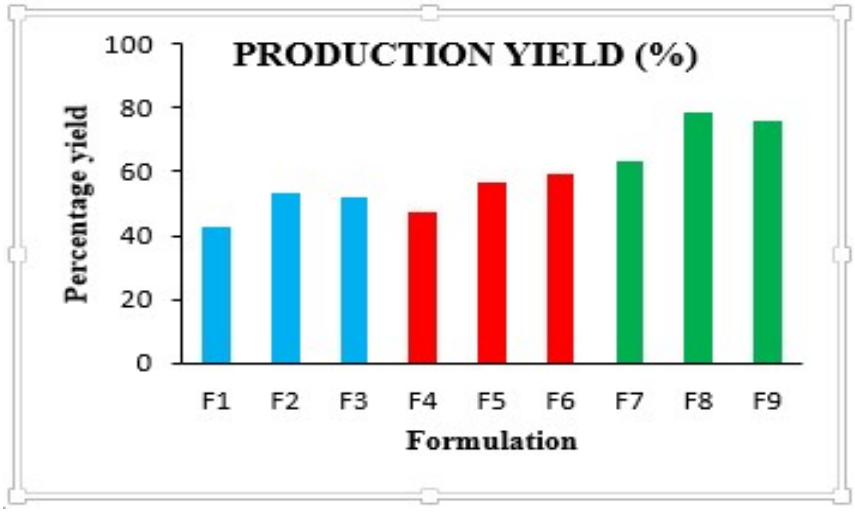


Fig 11: production yield (%)

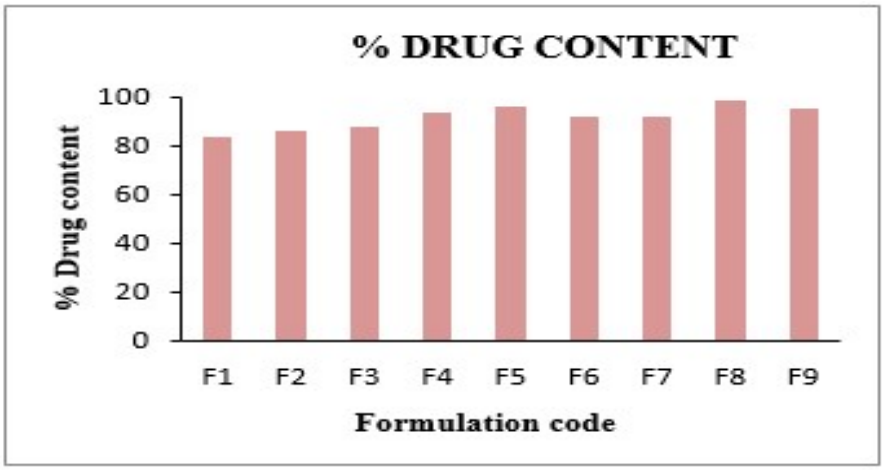


Fig 12: % of Drug content

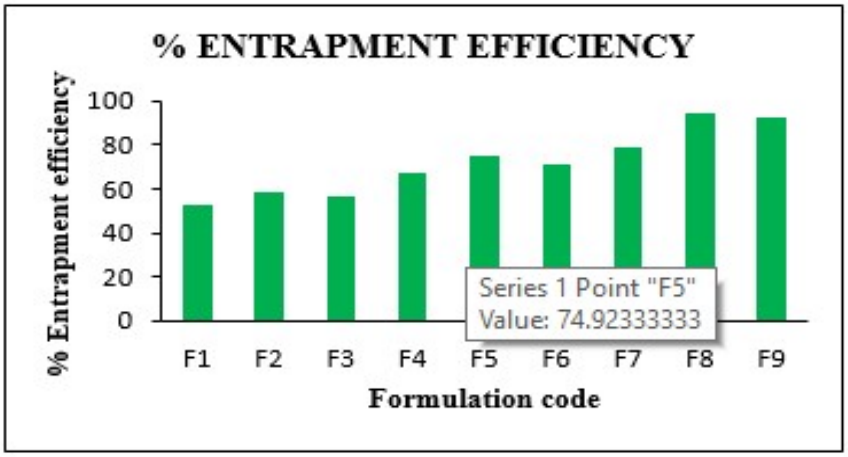


Fig 13: % of drug Entrapment Efficiency

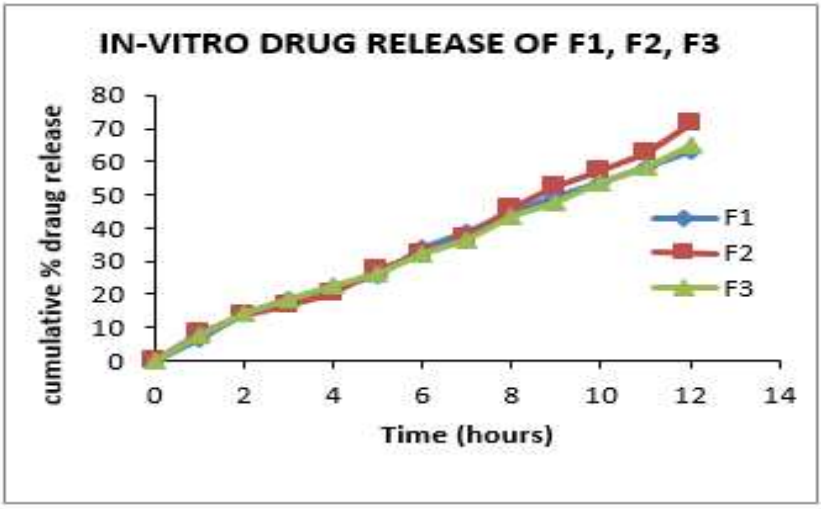


Fig 14: *In-vitro* drug release of F1, F2, F3

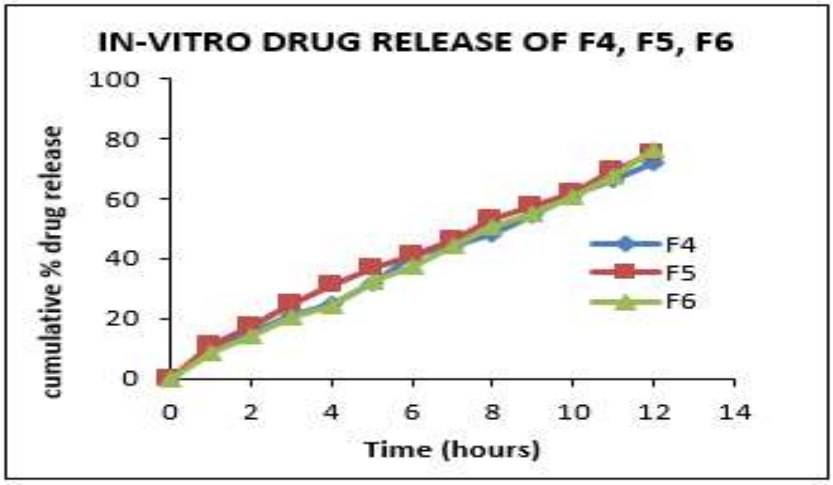


Fig 15: *In-vitro* drug release of F4, F5, F6

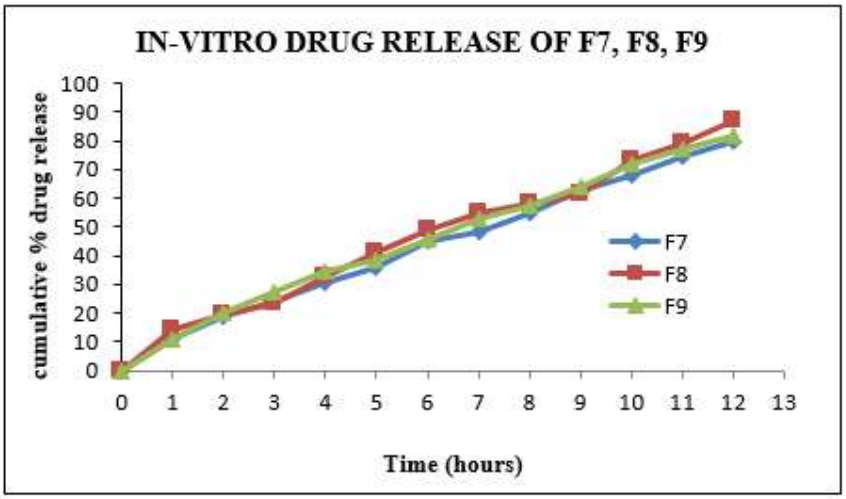


Fig 16: *In-vitro* drug release of F7, F8 and F9

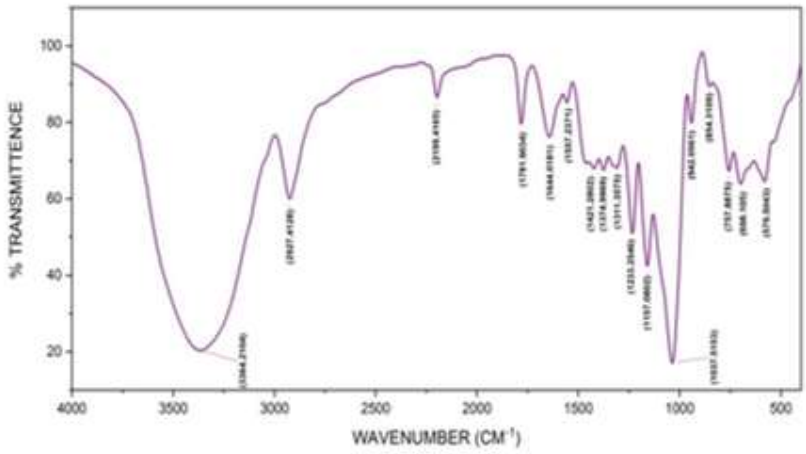


Fig 17: FT-IR spectrum of Formulation F8

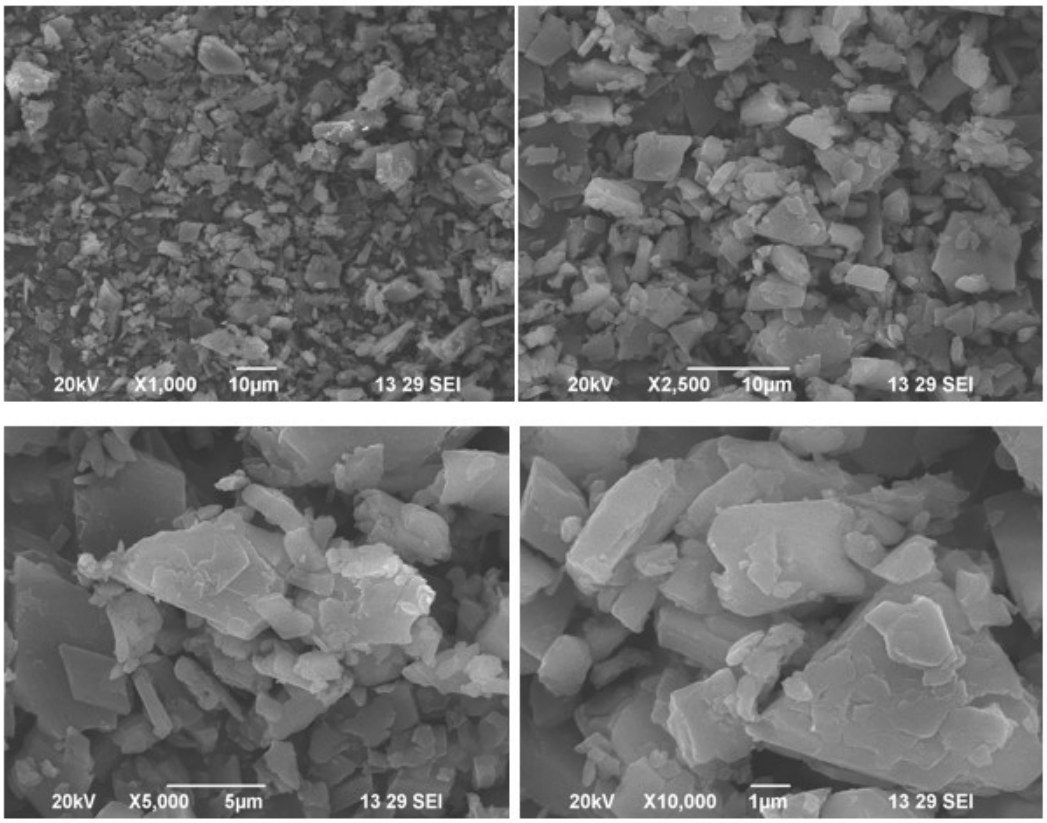


Fig 18: SEM images of luliconazole nanosponge

			Size (d.nm):	% Intensity	Width (d.n...
Z-Average (d.nm):	510.5	Peak 1:	568.8	92.6	183.7
PdI:	0.387	Peak 2:	132.5	7.4	27.14
Intercept:	0.888	Peak 3:	0.000	0.0	0.000

Result quality : Refer to quality report

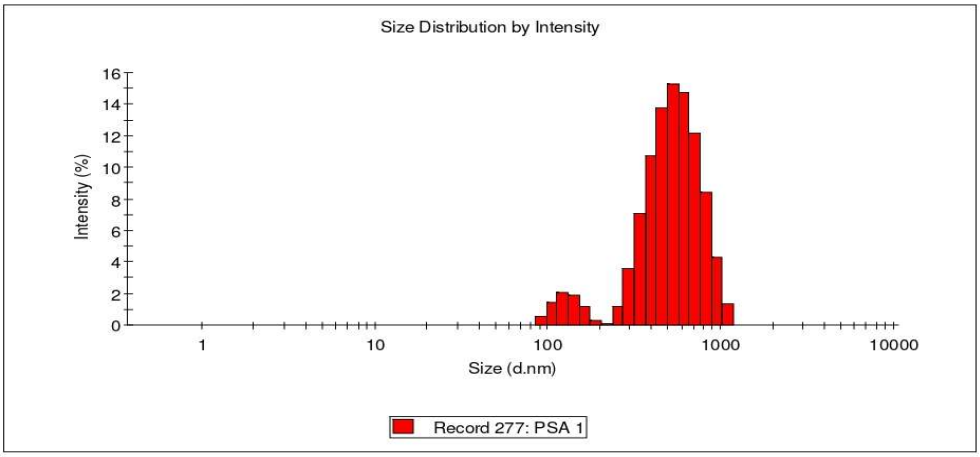


Fig 19: Particle size of Luliconazole Nanosponge

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -14.1	**Peak 1:**	-2.96	43.6	5.81
Zeta Deviation (mV): 14.0	**Peak 2:**	-17.2	39.1	5.65
Conductivity (mS/cm): 0.0582	**Peak 3:**	-34.4	13.8	4.25

Result quality : See result quality report

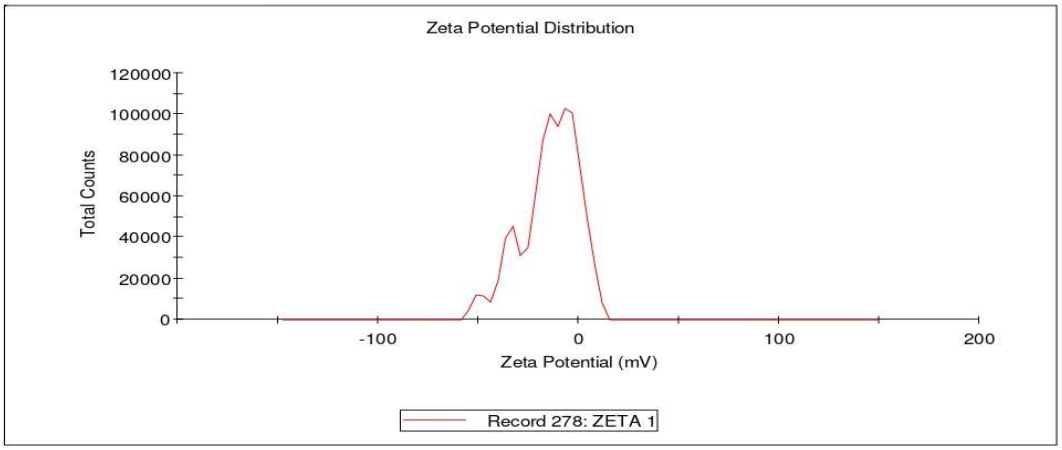


Fig 20: zeta potential of LuliconazoleNanosponge

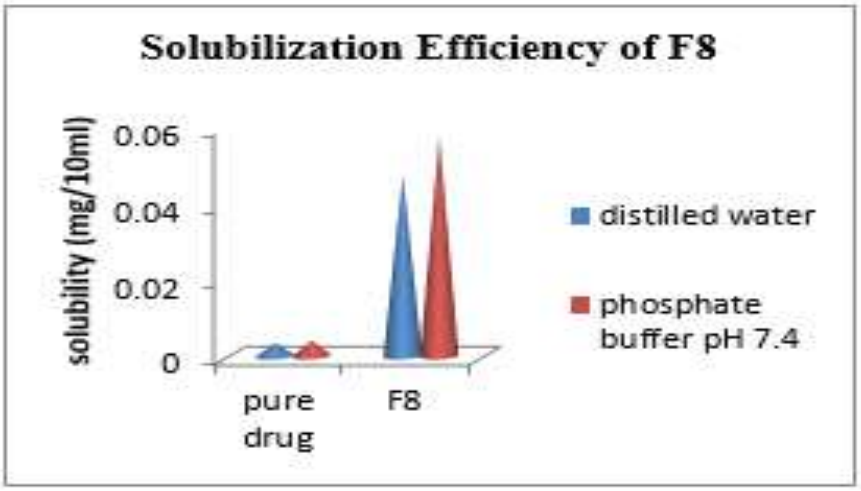
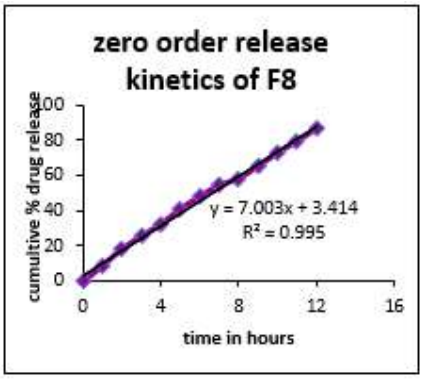


Fig 21: Solubilization Efficiency



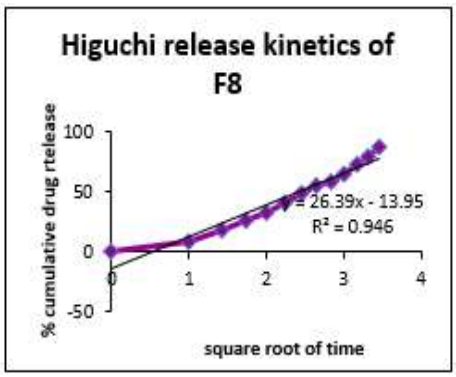


Fig 22: zero order kinetics of F8 **Fig 23: Higuchi's model of F8**

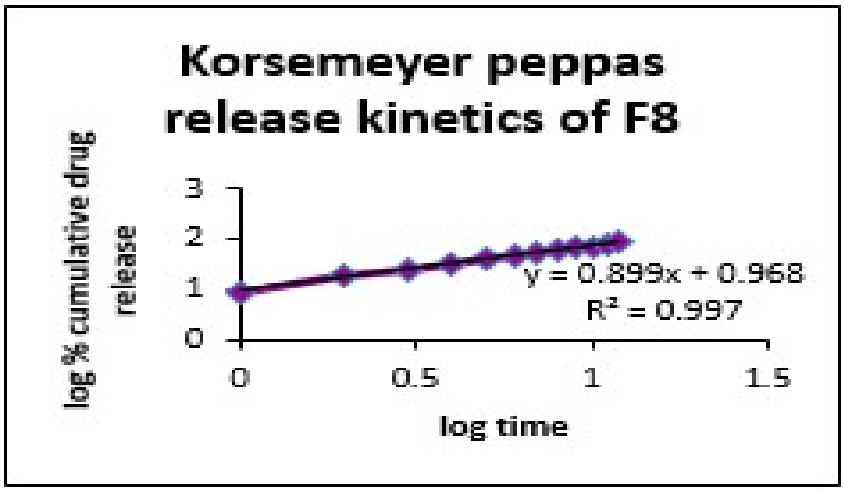


Fig 24: korsemeyerpeppas model of F8

Fig 25: luliconazole nanosponge gel

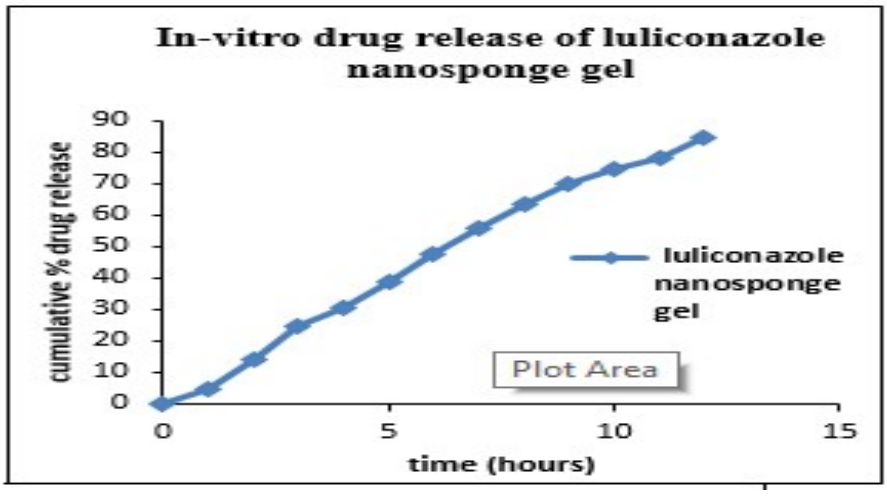


Fig 26: *In-vitro* drug release of Luliconazolenanosponge gel

Figure 27: A-Zone of inhibition of control, B-Zone of inhibition of marketed cream, C-Zone of inhibition of luliconazole nanosponge gel.

CONCLUSION

Nanosponge systems have been found to have good potential for prolonged drug release and therefore it can be beneficial for use in the treatment of various chronic fungal infections. The results obtained from this study revealed that prepared luliconazole loaded hydrogel enhanced the aqueous solubility and has a great potential to improve the topical delivery of drug as compared with conventional cream. Therefore, it was concluded that luliconazole loaded formulation has a enormous potential for topical delivery with better controlled drug release and antifungal activity for the treatment of superficial fungal infections. In conclusion luliconazole loaded nanosponge hydrogel could be a novel approach which can be applied in future to improve the dermal delivery of drugs with poor aqueous solubility. However further studies are needed to fully explore these formulations such as considerable pharmacokinetic studies, in-vitro skin permeation study, histo pathological studies and toxicity studies.

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CONFLICTS OF INTEREST

There are no conflicts of interest regarding the publication of this article to disclose.

AUTHOR'S CONTRIBUTIONS

All authors contributed to the preparation of the final manuscript.

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