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Design and Characterization of Nystatin Solid Dispersion for Improved Treatment of Fungal Infections

Rahul Kumar Jain[a*] and Rahul Trivedi

[a] Research Scholar, B.R.Nahata College of Pharmacy, Faculty of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh- 458001, India.

[b] B.R.Nahata College of Pharmacy, Faculty of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh- 458001, India.

***Corresponding author:**Rahul Kumar Jain, rkjain84@gmail.com

ABSTRACT:

The objective of present research work was to develop solid dispersion of Nystatin by using different concentrations of drug and polymer ratio. The effect of different concentrations of polymers was determined on the drug content and percentage cumulative drug release. Drug release followed zero-order models and mechanism of drug release are independent on the concentration of a drug. The optimized formulation NST-SD-7 is demonstrated particle size 41.24 micrometer, cumulative drug release 99.65±2.12 and drug content of 99.71±3.28 %.Scanning Electron Microscopy reveled optimized NST-SD-7 was spherical in shape having smooth surfaces. Antifungal studies conformed that NST-SD have better efficacy in treating *Candida Albicans* as compared to *Aspergillus flavus*. From the results we may conclude that NST-SD can be used as competent alternative to treat fungal infection caused by *Candida Albicans* as compared and *Aspergillus flavus*. However; further *in vivo* studies are required to establish its efficacy against fungal infections.

Keywords: Soliddispersion, Nystatin, Anti-fungal, Candida Albicans and Aspergillus flavus etc.

Introduction

Fungal diseases affecting the skin and nails are the most prevalent in humans, impacting approximately 25% of the global population, or 1.7 billion people, with these infections.[1] The fungal infections that fall under these broad categories vary in terms of the

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traits of the causing organisms, their epidemiology, the clinical presentation, the method of diagnosis, and the guiding principles of treatment.[2] Opportunistic fungal infections are primarily caused by Candida species, and fluconazole or an echinocandin antifungal agent are typically used to treat bloodstream infections. Most invasive mold infections are caused by Aspergillus species; they are associated with a high mortality rate and primarily cause pulmonary and sinus infections in older adults.[3] When the mold form is spread and inhaled from the surroundings in those particular regions of the nation where these organisms flourish, the endemic fungi Histoplasma capsulatum, Coccidioides species, and Blastomyces dermatitidis cause infection.[4]

Nystatin is a polyene antifungal antibiotic obtained from Streptomyces nursei. It is having broad spectrum antifugal activity against *Candida*, *Aspargilus niger*, *yeasts* and moulds. Instead of having potential antifungal potential its efficacy inhibited by its poor water solubility and low bioavailability. Nystatin has no injectable formulations due to toxicity profile. However, Nystatin may be given safely by orally Mucocutaneous membrane due to low absorption through skin and gut membrane.[5]

Ample of approaches have been used to improve the solubility and dissolution rate of poorly water soluble drugs such as reduction of crystals size, conversion of drugs into prodrugs, use of amorphous forms, cosolvation and superdisintegrants, impregnating liquid drugs or drug solution in porous powders, using surface active self-emulsifying systems, micronization, formation of inclusion complexes with cyclodextrin, formation of amorphous drug, and formation of solid dispersion (SD) with hydrophilic carriers.[6]

Solid dispersions (SD) is now firmly established as a platform technology for the formulation of poorly soluble drugs.[7] SD is defined as dispersion of drug in an amorphous polymer matrix where the drug is preferably in the molecularly dispersed state.[8] These systems were defined as the dispersion of one or more active ingredients in an inert matrix in the solid state prepared by melting (fusion), solvent or melting solvent method with the goal of enhancing oral bioavailability.[9-10] SD attributed to faster carrier dissolution, releasing microcrystals or particles of drug. These SDs, which could be designated as first-generation SDs, were prepared using crystalline carriers. Crystalline carriers include urea and sugars, which were the first carriers to be employed in SDs.[11] They have the disadvantage of forming crystalline SDs, which were more thermodynamically stable and did not release the drug as quickly as the amorphous ones. Various methods were employed for preparation of SDs, namely, solvent evaporation method, melt extrusion, spray drying, coprecipitation,

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fusion method, melting method, supercritical fluid methods, etc.[12] The aim of the current study was to develop and characterize SD of nystatin (NST-SD) to improve solubility and antifungal efficacy.

Materials and Methods

Materials:

Nystatin was kindly gifted by Lifecare Innovations Pvt. Ltd. Vadodara, India. PVP K25,PVP K90 were procured from Evonik Industries, Mumbai, India, PVA was procured from Loba Chem. Pvt. Ltd, Mumbai, India. PEG 4000 was obtained from SDFCL Ltd. Mumbai. All chemicals and ingredients used were of analytical grade.

Drug-Excipient Compatibility study

FTIR Spectroscopy

In the development of formulation drug and polymer are in close contact with each other and the stability of developed formulations depends on these interactions. Drug sample and polymer sample mixed with potassium bromide and FTIR spectra were taken. Shifting or disappearance of drug peak was studied.[13]

X-Ray Diffraction

For characterization of crystalline state, the X-ray diffraction pattern of drug alone and in combination with Eudragit RS-100 and Ethyl cellulose were determined using X-ray diffractometer with a copper target, at a current of 20 MA and a voltage of 40 kV. The rate of the scanning was 0.30 °C /min. [14]

Differential Scanning Calorimetry (DSC)

DSC is commonly used calorimetric techniques employed to characterize the physical state of drug and solubility in the complex. Thermo grams of the drug and a mixture of drug, Eudragit

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RS-100 and Ethylcellulose were recorded using a differential scanning calorimeter and were compared. 5 mg of sample was sealed in aluminum pans which are flat bottomed and heated at a temperature range of 100-300 °C at a rate of 10 ° k/min using alumina as a reference standard. [15]

Preparation of Solid Dispersions

Solid dispersion of nystatin was prepared by melting and solvent method. The composition is shown in table No:1. In melting method the drug and carrier PVP K25, PVP K90 and PEG 4000 were mixed in 1:1, 1:2, and 1:3 ratios in a china dish and heated on a paraffin bath. The mixture was poured on a tile and cooled. The resulted solidified mass was dried pulverised and passed through sieve # 100. In solvent evaporation method, the drug and carrier PVP K25, PVP K90 and PEG 4000 were mixed in 1:1, 1:2 and 1:3 ratios in methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100. [16]

Evaluation of NST-SD

Solubility Studies

Phase and saturation solubility studies were conducted as per the method described by Higuchi *et al*. The saturation solubility of drug, physical mixtures, and SD in distilled water and 0.1N HCl was determined by adding an excess of drug, physical mixture, and SD to 50 mL distilled water and 0.1N HCl in a conical flask (Glassco, Delhi, India) and were shaken on rotary shaker (Remi Elektrotechnik Ltd, Mumbai, India) for 72 h at 37°C ± 0.5°C. The saturated solutions were filtered through a 0.45-µm membrane filter (Membran Filter India Pvt, Ltd. Maharashtra, India), suitably diluted with water, 0.1N HCl, and analysed using Shimadzu UV-1900 Shimadzu, Kyoto, Japan) UV-1601 spectrophotometer at 322 nm.[17]

Surface morphology of NST-SD

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Surface morphology and topography was best studied by using scanning electron microscopy (SEM). Gold palladium was used to coat the developed sample of microsponge under an argon atmosphere at room temperature and surface morphology was studied with SEM. [18]

Particle size determination

Optical microscopy is used for the particle size determination of NST-SD developed formulations. The Optical microscope was fitted with an ocular micrometer and a stage micrometer. The eyepiece micrometer was calibrated. 50 particles were measured randomly by optical microscope for diameter. [19]

Dug content

Prepared NST-SD was assayed spectrophotometrically at 322 nm for the drug content at the maximum wavelength with proper dilution of formulations taking ethanol: water (1:1) ratio as blank. [20].

In vitro drug release studies

The invitro dissolution studies were done to compare the rate of dissolution of NST-SD with that of pure drug nystatin. The test was performed in USP paddle apparatus using 900 ml phosphate buffer solution at pH 7.4 and temperature 37+ 2 ^{0}C. [21]

Antifungal Activity by Disc Diffusion Method

Brain Heart Infusion agar media is used and bring agar plates to room temperature before use. Using a loop or swab, transfer the colonies to the plates. Visually adjust turbidity with broth to equal that of a 0.5 McFarland turbidity standard that has been vortexed. Alternatively, standardize the suspension with a photometric device.Within 15 min of adjusting the inoculum to a McFarland 0.5 turbidity standard, dip a sterile cotton swab into the inoculum and rotate it against the wall of the tube above the liquid to remove excess inoculum. Swab entire surface of agar plate three times, rotating plates approximately 60 º between streaking to ensure even distribution. Avoid hitting sides of the Petri plate and creating aerosols. Allow the inoculated plate to stand for at least 3 minutes but no longer than 15 min. before making wells. Prepare the stock solution weighing 10 mg of the compound and dissolve it in 1ml of DMSO.Take a hollow tube of 5 mm diameter, heat it. Press it on above inoculated Agar plate and remove it immediately by making a well in the plate. Likewise, make five well on each

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plate. With the help of micropipette add 75 µl, 50 µl, 25 µl, 10 µl, and 5 µl in each well.Incubate plates within 15 min of compound application. Invert plates, and stack them no more than five high. Incubate for 18-24 h at 37 ºC in the incubator. Read plates only if the lawn of growth is confluent or nearly confluent. Measure the diameter of the inhibition zone to the nearest whole millimeter by holding the measuring device. [22]

MIC Test

9 dilutions of each drug have to be done with BHI for MIC. In the initial tube 20microliter of drug was added into the 380microliter of BHI broth. For dilutions 200microliter of BHI broth was added into the next 9 tubes separately. Then from the initial tube 200microliter was transferred to the first tube containing 200microliter of BHI broth. This was considered as 10-1 dilution. From 10-1 diluted tube 200microliter was transferred to second tube to make 10-2 dilution. The serial dilution was repeated up to 10-9 dilution for each drug. From the maintained stock cultures of required organisms, 5microliter was taken and added into 2ml of BHI (brain heart infusion) broth. In each serially diluted tube 200microliter of above culture suspension was added. The tubes were incubated for 24 hours and observed for turbidity. [23]

Stability study

Following ICH recommendations Q1A (R2), a stability study has been performed. It was kept in a stability chamber at a temperature of 40 ± 2 °C and 75 ± 5% RH for 90 days. Different parameters like drug content (%), cumulative drug release (% CDR) were examined at specified time intervals (1, 2 and 3 months). [24]

Results ad Discussion

3.1. Solubility Studies

Solubility studies were performed to identify suitable vehicles with maximum potential to soubise the drug and having good miscibility with each other which helps in minimizing the final volume of SD. The results of saturation solubility studies are given in Figure 1. The solubility of pure NST in water and in 0.1N HCl was found to be 1.54 ± 0.14mg/mL and 1.71 ± 0.18 mg/mL, respectively. The solubility NST-SD using PVPK-25 , PVPK-90 and PEG-4000 in the ratio (1:1, 1:2, and 1:3) was 42.85 ± 3.11 mg/mL, 31.64 ±2.45 µg/mL, and 35.44 ± 2.65 mg/mL, respectively, in water and 48.24 ± 3.67 mg/mL, 34.17 ± 4.75 mg/mL, and 39.42 ± 3.74 mg/mL, respectively, in HCl. These results revealed

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that solubility of NST was enhanced with SD using PVPK-25 when compared to PVPK-90 and PEG-4000. [25]

Compatibilities Studies:

Nystatin, PVP K-25, PVP K-90 and NST-SD were analyzed by infrared spectroscopy for knowing purity and to characterize the probable structural modification of the drug sample. The sample was analyzed in the region of 4000 and 400 cm-1. FTIR of Nystatin shows specific peaks related to specific structural features as follows, - C=C stretch at 1635.47, C-H stretch at 3462.63, C=C at 1449.86, CO stretch at 1112.67 and CARBONYL stretch at 1449.86 and cm− 1.The values are near or equal to values mentioned in standard structure of nystatin. FTIR spectra of NST-SD formulation characteristic peaks as follows, C=C stretch at 1632.87, C-H stretch at 3343.65, C=C at 1423.44, CO stretch at 1218.32and CARBONYL stretch at 1598.77 cm− 1. It revealed that the fundamental peaks of the nystatin are retained in the SD formulation. Results showed that there exist no chemical interaction between nystatin and excipients used and were found to be compatible. [26]

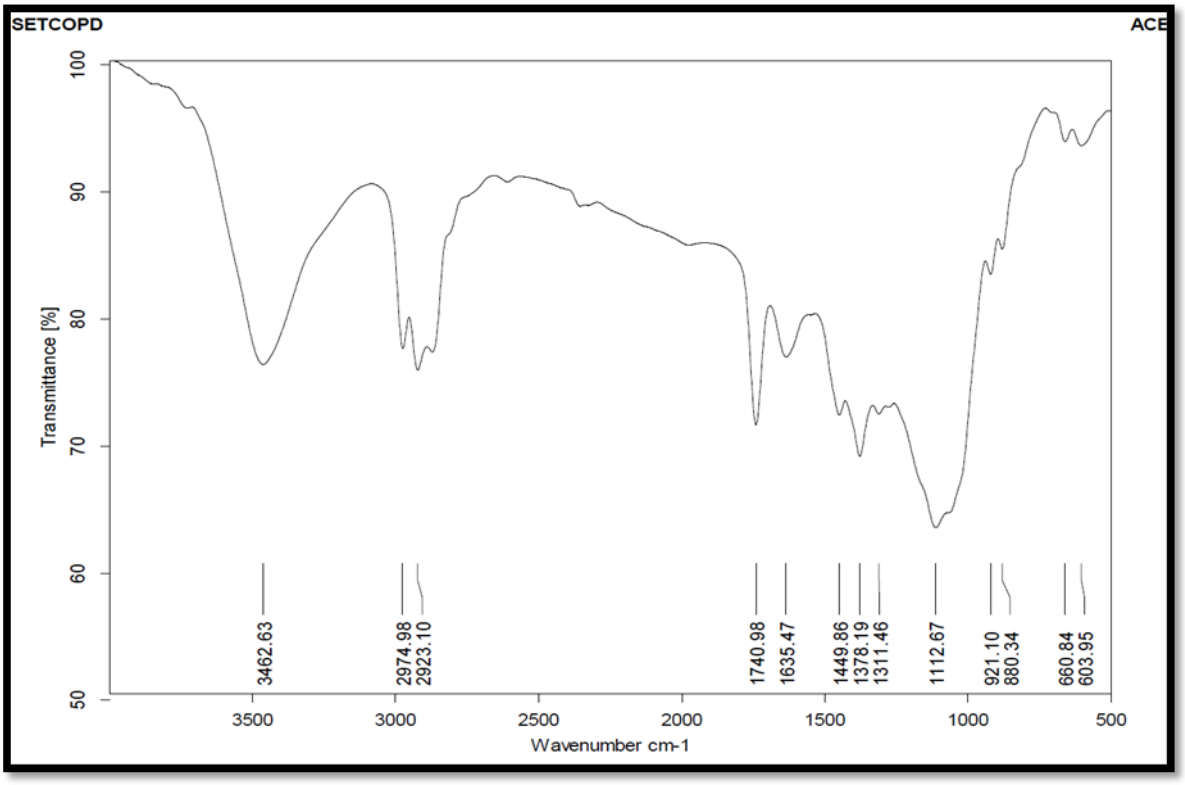

Fig.1A: FTIR Spectra of Nystatin

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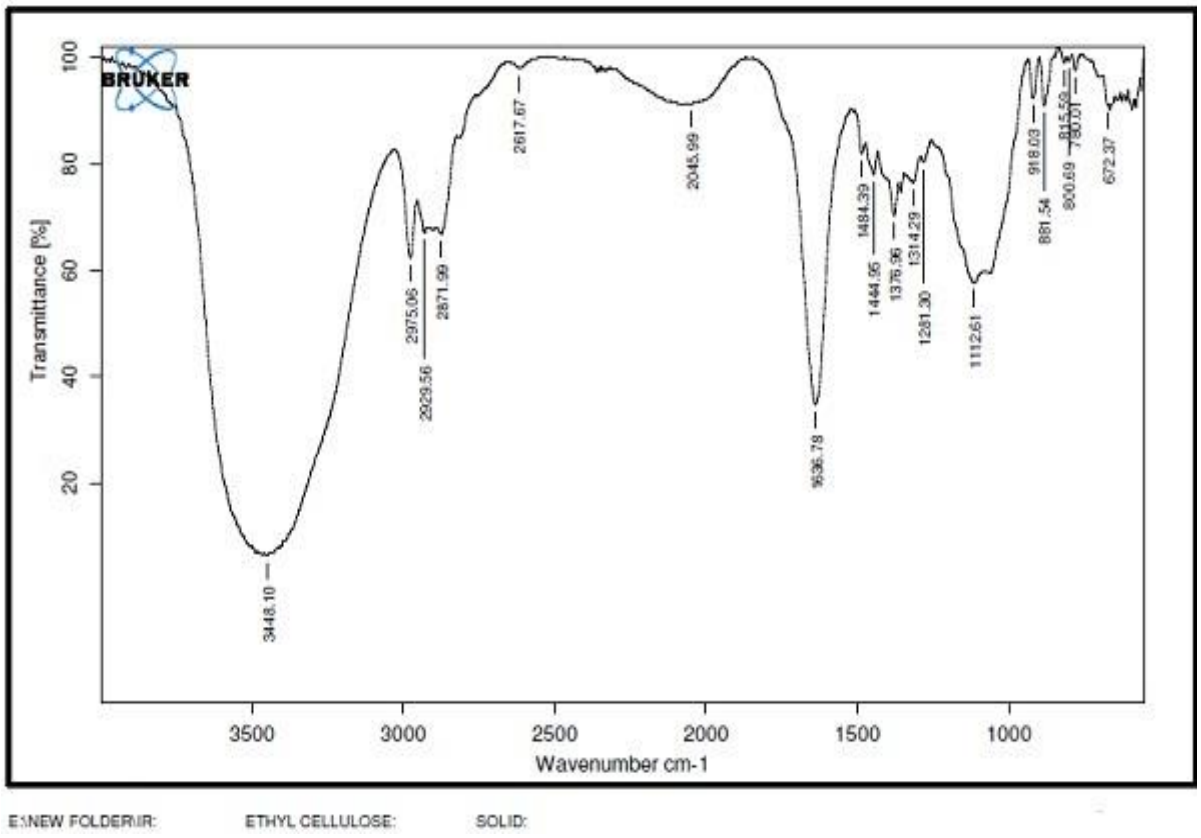

Fig.1B: FTIR Spectra of PVP K-25

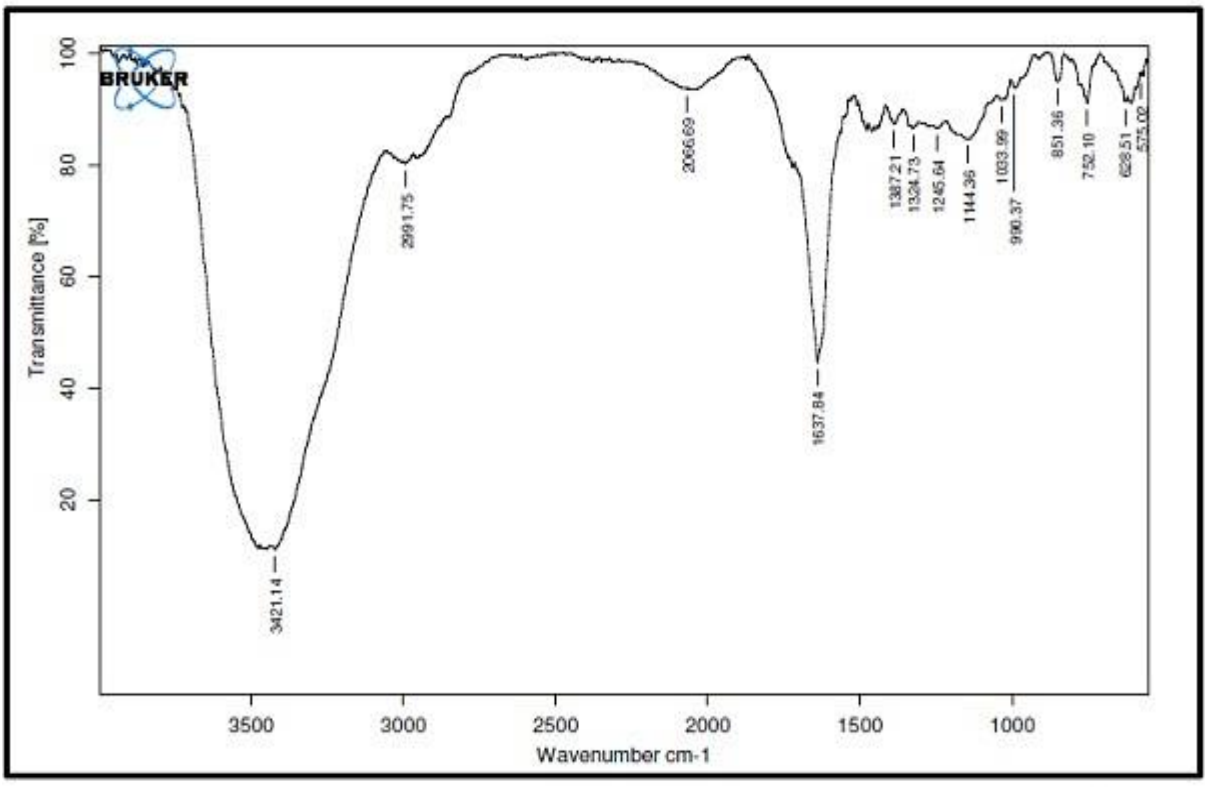

Fig.1C: FTIR Spectra of PVP K-90

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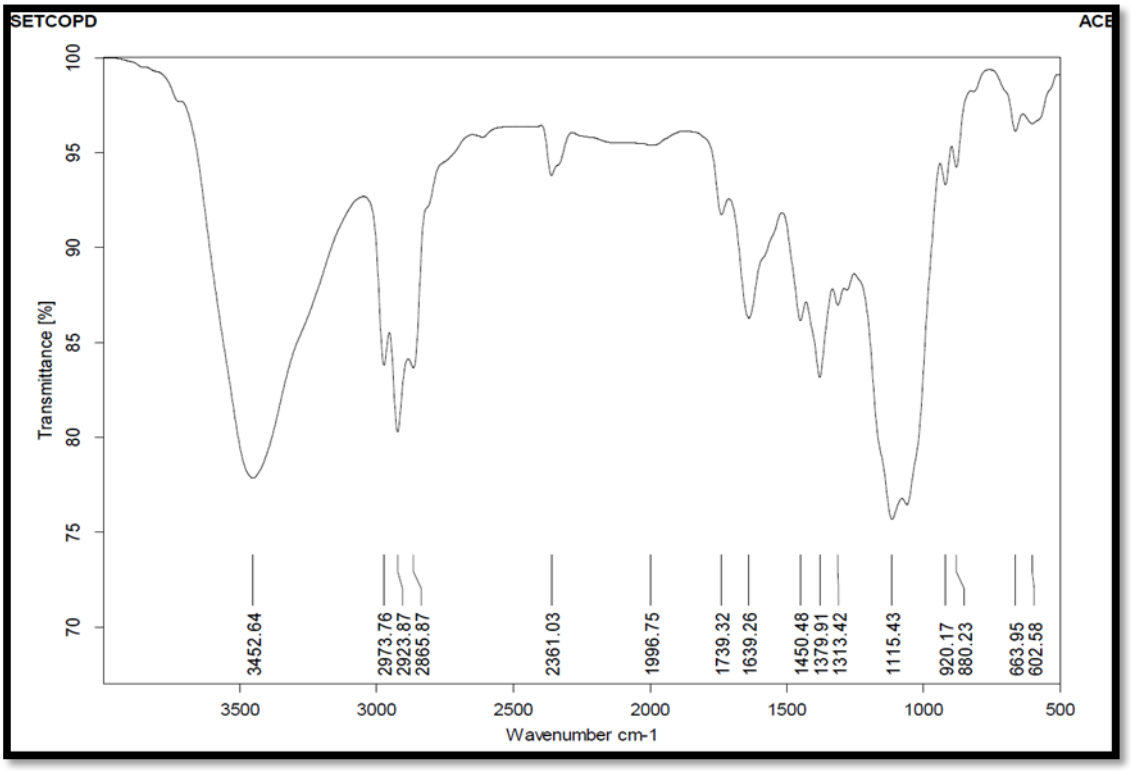

Fig.1D: FTIR Spectra of Optimized NST-SD-7

XRD Studies:

X-ray diffraction studies were carried out to confirm the physical state of NST-SD in comparison to nystatin and PVP K-25. It is clear that the diffractogram of the nystatin exhibited characteristic intensity sharp peak reflections, indicating its crystalline nature. However, these characteristic peaks disappeared in the X-ray diffraction pattern of NST-SD. Results conformed molecular dispensability of nystatin in to SD from crystalline to amorphous form. [27]

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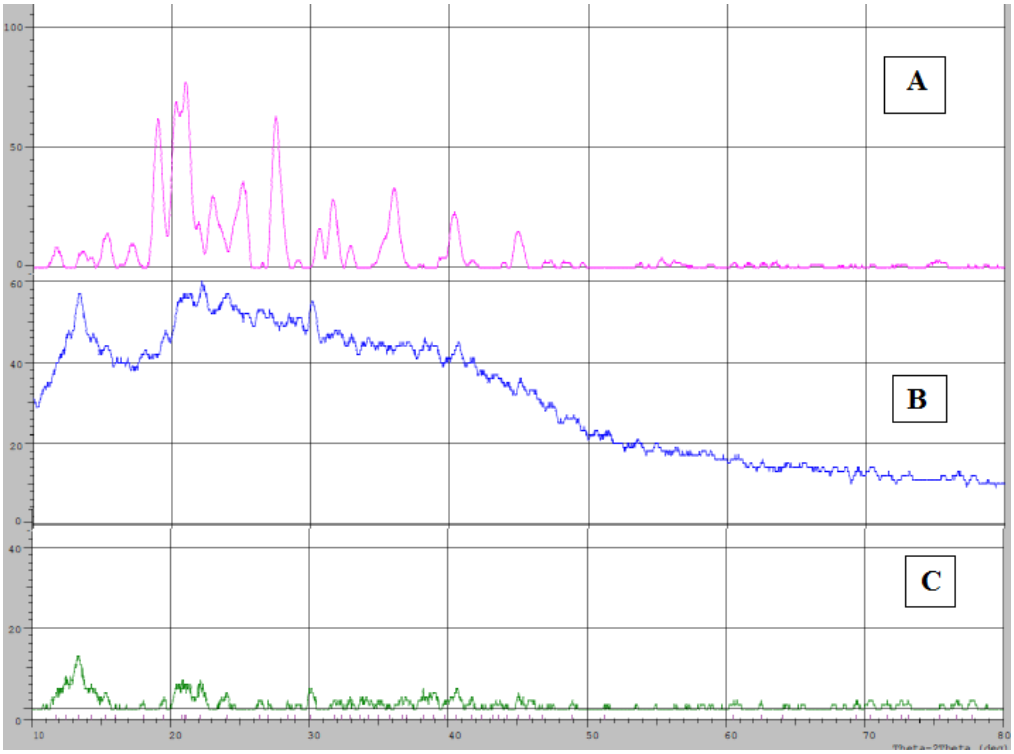

Fig.2: XRD Spectra of A) NST B) PVP C) Optimized NST-SD-7

Scanning Electron Microscopy (SEM) of NST-SD

Scanning electron microscopy was used to determine surface morphology. SEM of NST-SD formulation showed that the surface was smooth with devoid cracks having spherical in shape. The SEM of NST-SD shown in Fig. 3

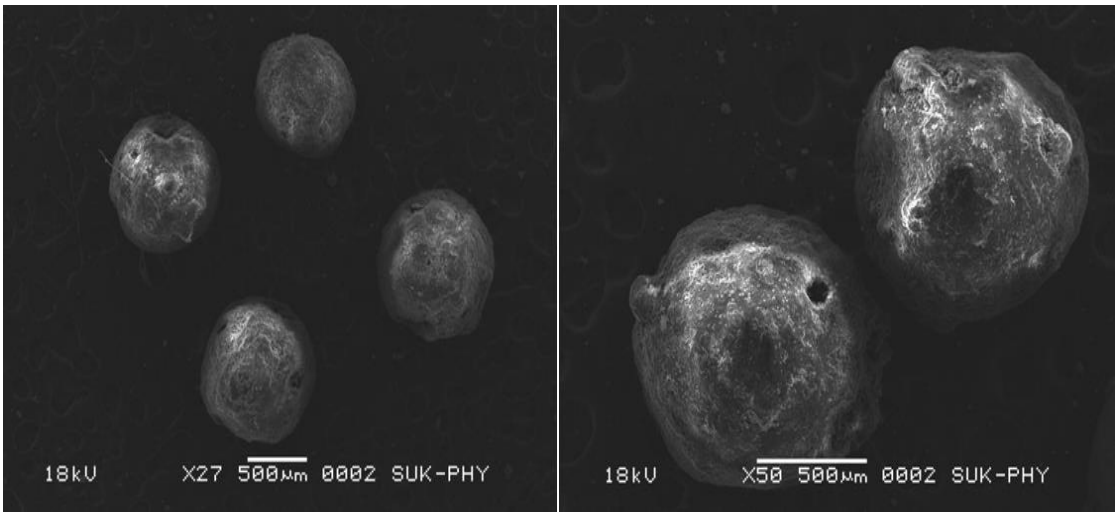

Fig. 3: SEM of NST-SD Optimized formulation

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Particle Size:

Particle size of Optimized NST-SD-7 formulation was found to be 41.25 µm.Having PDI 0. 346.Results were shown in Fig.4.

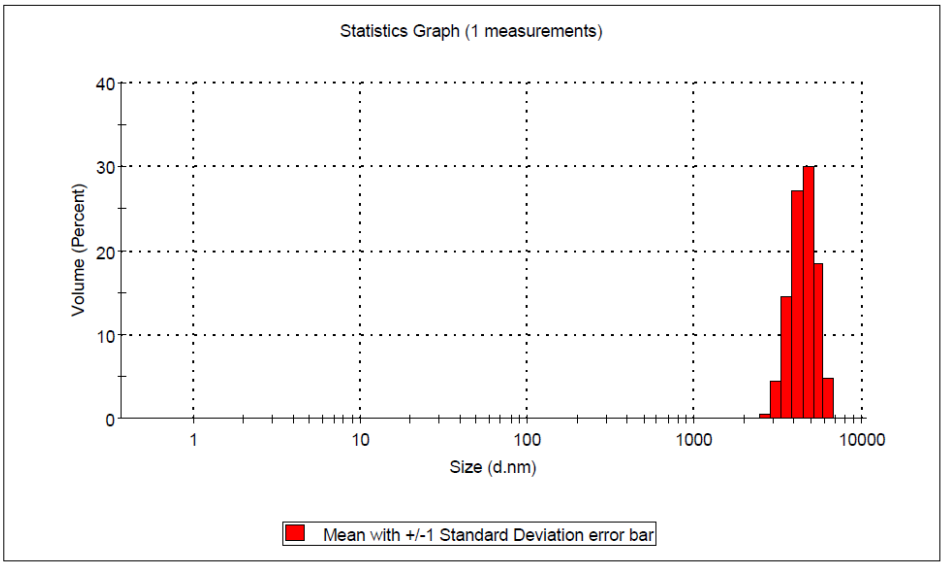

Fig. 4: Particle Size of Optimzed NST-SD formulation

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Table 1. Full factorial Design matrix summarizing the levels, factors, and responses of 09 runs for optimization of Nystatin Solid Dispersion (NST-SD)

Run	Block	Factor 1 Polymer	Factor 2 (X2) (Drug: Polymer Ratio)	Cumulative Drug Release (Y1)	Drug Content (Y2)
1	NST-SD-1	K25 (-1)	1:1 (-1)	82.43±4.32	82.23±3.54
2	NST-SD-2	PEG (0)	1:1 (-1)	79.12±4.32	78.43±3.32
3	NST-SD-3	K90 (1)	1:1 (-1)	78.32±5.87	84.52±2.65
4	NST-SD -4	K25 (-1)	1:2 (0)	91.65±2.41	90.32±4.73
5	NST-SD-5	PEG (0)	1:2 (0)	87.67±3.82	92.45±3.17
6	NST-SD-6	K90 (1)	1:2 (0)	88.76±3.88	94.15±2.14
7	NST-SD-7	K25 (-1)	1:3 (1)	99.65±2.12	99.71±3.28
8	NST-SD-8	PEG (0)	1:3 (1)	94.42±4.43	96.08±3.54
9	NST-SD-9	K90 (1)	1:3 (1)	92.23±3.34	97.48±2.72

Factor	**Levels used, actual (coded)**		
	Low (-1)	Medium (0)	High (+1)
Independent variables			
Factor 1 (X_1) (Polymer)	PVP K-25	PEG-4000	PVP K-90
Factor 2 (X_2) (Drug: Polymer)	1:1	1:2	1:3
Dependent variables			
Drug Release (Y_1)	**Maximize**		
Drug content (Y_2)	**Maximize**		

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Drug Release profile:

In-vitro dissolution of NST was studied using phosphate buffer (pH 6.8) as dissolution medium. Enhanced dissolution rate of NST was attained in all cases. Dissolution rate of the prepared SD significantly exceeded the plain drug NST (Table 1). Plain drug showed significantly sluggish and incomplete dissolution (27.34 ±2.5%) within the total dissolution time (one hour (h)). However, dissolution of all systems almost reached completion at the end of dissolution time. The maximum and minimum drug dissolved were found to be for NSD-SD-7 and NSD-SD-2 99.65±2.12 and 79.12±4.32 respectively after 60 minutes. Results showed that the highest dissolution was achieved from systems prepared at 1:3 (w/w) D:P ratio, whereas the least dissolution was obtained from systems prepared at 1:1 (w/w) D:P ratio. Also results revealed that PEG 8000 based SD systems displayed superior dissolution rates compared to other prepared systems. Improved dissolution rate of NST within the prepared systems can be attributed to several factors including incorporation of strongly hydrophilic polymers to enhance drug's wettability. Enhanced wetting properties of hydrophobic NST resulted in localized enhancement of its solubility within the diffusion layer surrounding drug particles. Similar results were obtained by El-nawawy et al. in their study on olmesartan solid dispersions. In addition, thesehydrophilic polymers are considered as precipitation inhibitors, where they produce a shell of hydration around drug molecules, preventing their aggregation. Moreover, they are able to form physically stable, soluble complexes with NST via intermolecular hydrogen bonding. NST contains one hydroxyl group which can form hydrogen bonds with carbonyl oxygen of the amide group in PVP molecules and ether oxygen in PEG molecules. Through hydrogen bond formation, polymers bind to the surface of drug particles preventing their nucleation and crystal growth. Sekizaki et al. and Turhan et al. confirmed hydrogen bond formation due to the presence of these functional groups in both polymers, respectively. It was also reported that stabilizing polymers as PVP acquire an antiplasticizing effect, providing decreased drug molecular mobility which inhibits drug nucleation/aggregation and hence contribute to drug amorphization . Finally, amorphous form of NST requires low energy to be dissolved where, reduced particle size increased surface area of drug particles subjected to dissolution medium. All these factors could contribute to enhanced dissolution profiles of NST within the prepared SD systems. [28]

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Drug Content

The mean percent of drug content ranged from 78.43±3.32 to 99.71±3.28 indicating as drug polymer ratio increases drug content also increases. Results are listed in Table 1. It means the drug and polymer has positive impact of drug content and vice versa. The maximum and minimum drug content were recorded by and NSD-SD-7 and NSD-SD-2 99.71±3.28 and 78.43±3.32 respectively. [29]

Antifungal activity: In-Vitro antifungal activity of NST and optimized NST-SD formulation carried out by disc diffusion method. Fungus species used for biological evaluation were *Candida albicans* and *A. fumigates.* Antifungal activity of NST and NST-SD was shown in Table 2 and Fig.00. Results showed that NST-SD showed greater zone of inhibition on *C. albicans* (34 mm) as compared to *A.Fumigatus* (30 mm) [30]

Table 2: Antifungal activity of Nystatin Microsponge (Zone of Inhibition Method)

Samples	75µl/ mL	50 µl/mL	25 µl/mL	10 µl/mL	5 µl/mL
Candida albicans					
NST	20mm	12mm	7mm	3mm	R
NST-SD	34mm	30 mm	28 mm	15 mm	R
A. fumigatus					
NST	18 mm	10mm	5mm	2mm	R
NST-SD	30 mm	28 mm	20 mm	15 mm	13 mm

Note: R-Resistant

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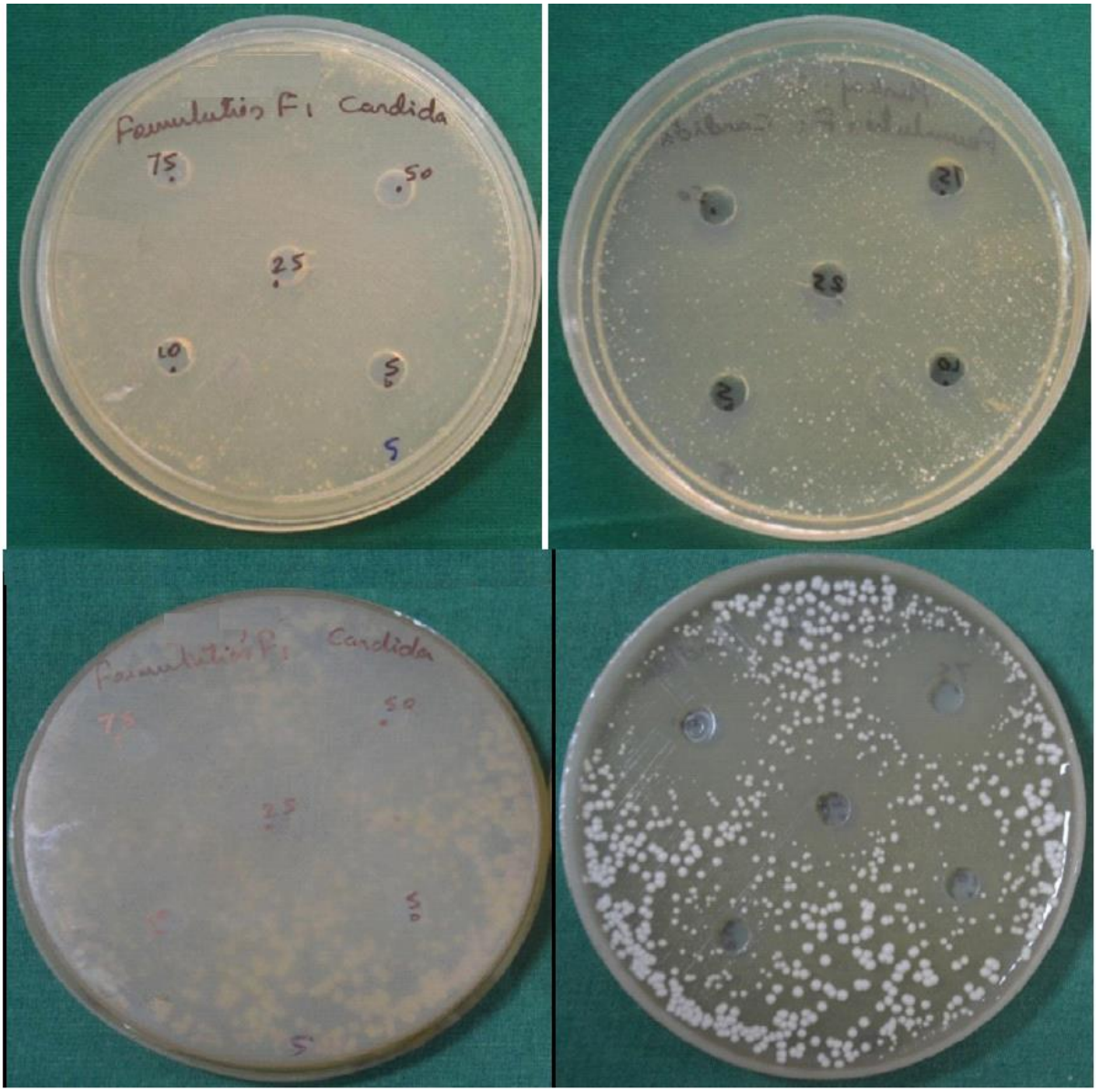

Fig. 5: Antifungal activity of optimized NST-SD on *C. albicans.* by Zone of Inhibition Method

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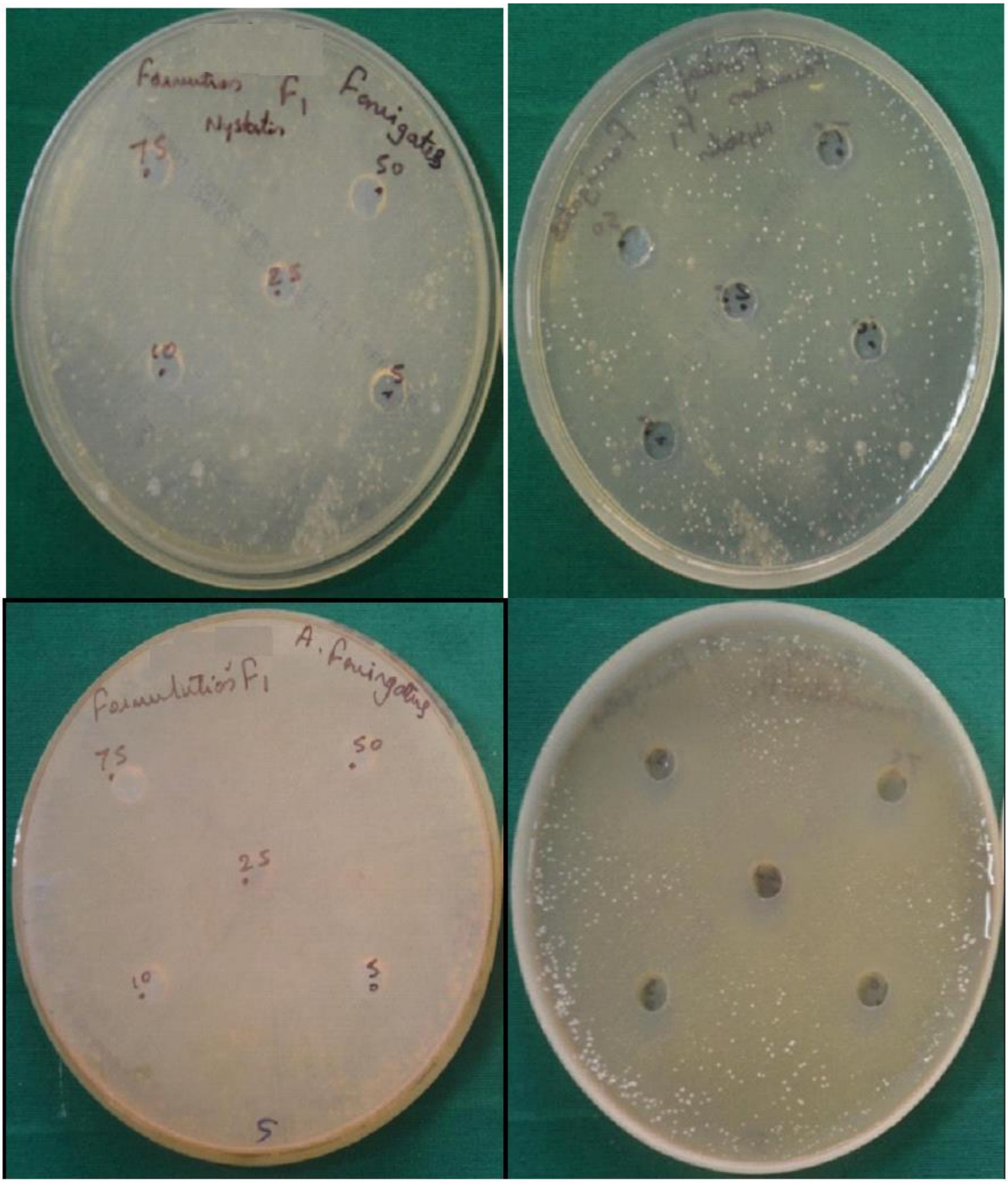

Fig. 6: Antifungal activity of optimized NST-SD on *A. fumegatus* by Zone of Inhibition Method

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MIC Results (Tube Dilution Method)

Minimum inhibitory concentration required to inhibit visual growth of an microorganism by drug is called MIC.MIC results showed that both organisms are sensitive at very low concentration of NST-SD when compared to pure NST.

Table 3: Antifungal activity of NST (Tube Dilution Method)

Samples	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml	0.4 µg/ml	0.2 µg/ml
NST										
C.albicans	S	S	S	S	S	R	R	R	R	R
A.flavus	S	S	S	S	R	R	R	R	R	R

Note: S- Sensitive, R- Resistant

Table 4: Antifungal activity of NST-SD (Tube Dilution Method)

Samples	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml	0.4 µg/ml	0.2 µg/ml
NST-SD										
C.albicans	S	S	S	S	S	S	S	S	R	R
A.flavus	S	S	S	S	S	S	S	R	R	R

Note: S- Sensitive, R- Resistant

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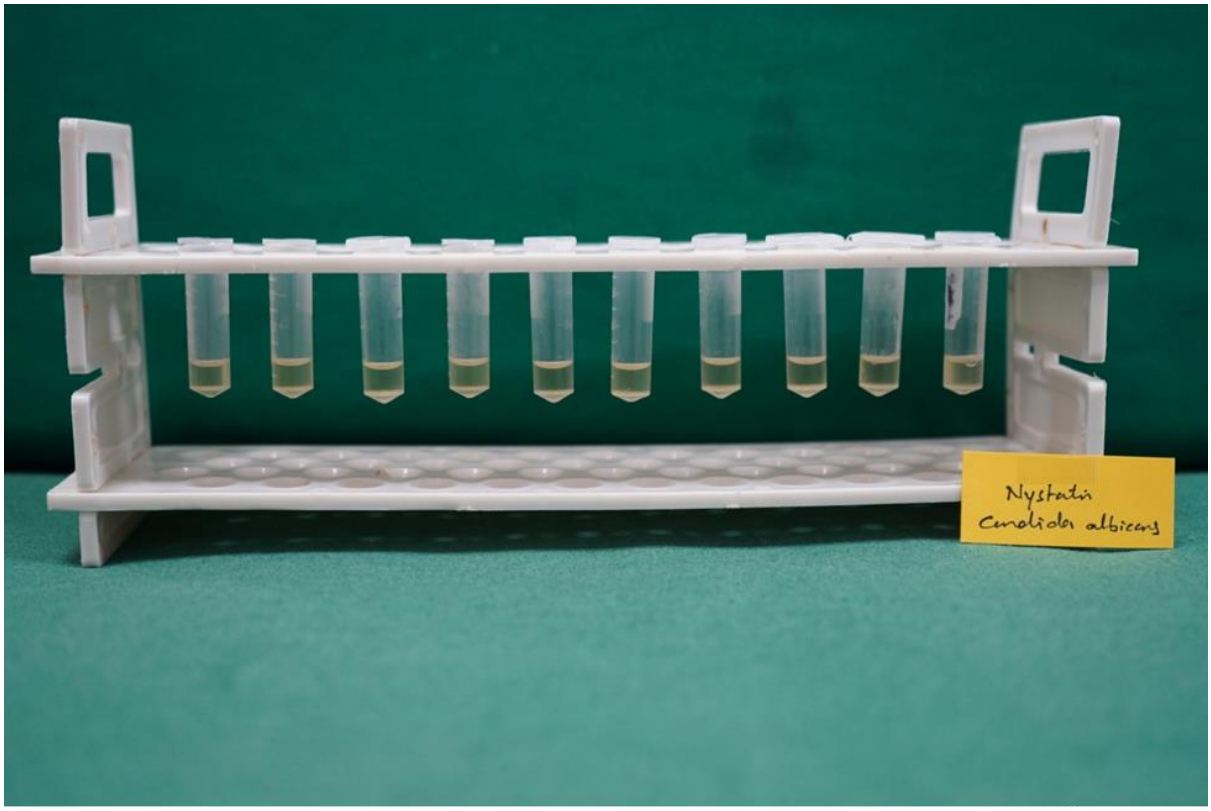

Fig.7: Antifungal Activity of Nystatin on *Candida albicans* by Tube Dilution Method

Stability Study

Stability studies were conducted on optimized formulation. The sample was stability studies conducted for 90 days. To determine how storage conditions affected drug content and cumulative drug releaseof a NST-SD, stability study was conducted. The properties of NST-SD did not change significantly ($p>0.5$) during storage. Results were shown in table 5.

Table 5: Accelerated Stability Study Data of optimized NST-SD

Evaluation parameter	At temp. 40°C ±0.5°C, RH75+5%			
	Initial	First Month	Second Month	Third Month
% CDR	99.83±1.05	99.72+0.82	99.61±0.72	99.58±0.83
% Drug Content	99.71±1.28	99.64+1.22	99.58 ±1.32	99.42 ±1.12

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Conclusions

From the results it is concluded that NST-SD was prepared by using different polymers such as PVP and PEG which enhances solubility and cumulative drug release of NST in the form of NST-SD. The in-vitro drug release study indicates that the release of NST from NST-SD formulations containing a varying concentration of polymer was inversely proportional. The higher release rate was found from prepared NST-SD from the lower concentration of polymer. SEM revealed that the surface of NST-SD was smooth and spherical with ideal surface morphology. In vitro antifungal studies conformed that NST-SD have better efficacy in treating *Candida Albicans* as compared to *Aspergillus flavus*. From the results we may conclude that formulations NST-SD 4 of Nystatin solid dispersion can be used as competent alternative to treat fungal infection caused by *Candida Albicans* as compared and *Aspergillus flavus.* However; further *in vivo* studies are required to establish its efficacy against fungal infections.

CONFLICT OF INTEREST:

All authors declare that they have no competing interests

AUTHOR'S CONTRIBUTIONS: .

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